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Pesticide Effects on Occupationally Exposed Workers:

A Summary of Four Years Observation of Industry and Farm Volunteers in South Carolina*

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Pesticides are necessary and of unquestioned economic value in agriculture, industry, and disease prevention. Their usage has increased astronomically in the last decade and will likely increase further in the future. Thus, the safe use of pesticides has become an increasingly important area for public concern. In response to this concern, the Preventive Medicine Section of The Medical University of South Carolina and The State Board of Health organized, in 1967, the South Carolina Community Pesticide Program to study the health effects, if any, of long-term pesticide exposure. The study team, composed of physician, biochemist, and entomologist, shaped in principle a partnership of industry and health professionals.

METHODS AND PROCEDURES

One hundred and twenty workers with mixed occupational exposures to pesticides averaging 12 years were compared with a control group over a four-year period. Since the intensity and type of pesticides used varied in the experimental population, the volunteers were grouped into six cohorts, as shown in Table 1, ranging from greatest (Cohort I) to least exposure (Cohort VI - Controls). Controls included employees from a roofing shingle manufacturing plant, a detergent producer, phosphoric acid plant, truck drivers, and firemen.

Medical and exposure histories were obtained from each participant as he entered the study and physical examinations were administered annually. This examination included chest x-ray, pulmonary function test, EKG, and blood pressure measurements, together with the usual physician's clinical evaluation.

At least once a year, but usually once a quarter, additional blood pressure readings were taken and blood and urine samples obtained for biochemical and residue profiles. Biochemical determinations included enzymes (SGPT, SGOT, LDH, alkaline phosphatase, CPK,

cholinesterases), kidney function tests (creatinine, uric acid, and BUN), glucose, total lipids, cholesterol, catecholamines, and protein electrophoresis. Other hematological tests, i.e., hemoglobin, hematocrit, and complete blood counts, were also performed. Pesticide residue detection was by gas chromatography. Urinalysis included microscopic examination, pH, albumin, glucose and blood. Stool specimens were also examined for blood, and urine and sputum cytologic examinations were made by a consulting pathologist.

Differences between cohort means were determined by Duncan's new multiple range test. When comparison was made of exposed groups with matched controls, a paired *t* test was used. χ^2 was employed to test differences in morbidity indices between exposed and control participants.

RESULTS AND DISCUSSION

Medical History and Physical Examination

Only arthritis (not specified as rheumatoid) and malaria appeared more frequently on the history of the pesticide exposed group. This difference seems to rest in the farmer group and may actually be a reflection of urban-rural differences in medical care. On the other hand, the control group recalled significantly more cysts and kidney disease and may indicate the better care

*Presented at the Southeastern Industrial Health Conference.

TABLE 1. Pesticide Exposure of Study Participants

<i>Cohort</i>	<i>Title</i>	<i>No. in Cohort</i>	<i>Predominant Pesticide</i>
I	Formulators	29	CH, OP, Car,
II	Pest control operators	20	CH, OP, Car,
III	Farmers	47	CH, OP, Car,
IV	Synthesizers	12	OP
V	Peripherally exposed	12	OP
VI	Controls	50	None

CH = Chlorinated Hydrocarbon; OP = Organophosphate;
Car = Carbamates

TABLE 2. Biochemical Tests Showing NO Difference Between Exposed and Control Cohorts**Blood**

Alkaline phosphatase
Creatinine phosphokinase
Lactic acid dehydrogenase
Serum glutamic oxalic transaminase
Blood Urea Nitrogen
Albumin
 α_1 , α_2 and γ globulins
Fasting blood glucose
Catecholamines (epinephrine, norepinephrine, metanephrine)
Urine pH, protein, occult blood, glucose, sp. gravity and osmolality

Stool guaiac

available to the more urban control group. Systems review analyses showed significantly more complaints among the control participants and may simply reflect motivational differences among volunteers. Pesticide workers may volunteer because the very nature of their work causes them concern, while industrial controls may be motivated to a similar level of health concern by the presence of minor symptoms or a hypochondriacal tendency.

There were no significant differences between exposed and control groups in physical findings, except that systolic blood pressure was elevated among formulators (Cohort I) and pest control operators (Cohort II). The most intensively exposed formulators and pest control operators (30 in number) were individually matched by age, race, sex, and physical activity with controls. Systolic and diastolic pressure, as well as serum cholesterol, were not only significantly elevated in the pesticide exposed workers, but correlated ($p < 0.05$) with plasma DDT and DDE. When examined by race, blood pressures and cholesterol were exaggerated in non-whites. A comparison of abnormal diastolic (>90 mmHg), systolic (>150), and a combination of both ($>150/90$) revealed an unusual incidence ($\chi^2, p < 0.005$)

of hypertension among the pesticide exposed subjects. Examination of medical records indicated no difference between these exposed and control groups or among races in smoking history, personal or family history of heart attacks, hypertension, diabetes, use of prescription drugs, and educational level. We would hasten to emphasize that although the statistically significant associations between blood pressure, cholesterol, and DDT blood levels are real, biological causality is unproved. DDT may only be an indicator of general pesticide exposure; in most instances, workers who handle DDT also come in contact with organophosphates, carbamates and other pest control chemicals, including solvents.

Table 2 lists blood and urine tests which yielded no consistent significant differences between pesticide exposed and control workers. Of particular interest is the indication that catecholamines may not account for elevations in blood pressure.

Table 3 presents a listing of biochemical values which were significantly different from control subjects in one or more cohorts of exposed volunteers.

Synthesizers and peripherally exposed groups are not exposed to DDT and, therefore, these findings are

**TABLE 3. Biochemical Tests Showing Significant Differences¹
Between Exposed and Control Cohorts**

	I Formulators	II PCO's	III Farmers	IV Synthesizers	V Peripherally Exposed
DDT	+	+	+	0	0
SGPT	+	+	+	+	+
ChE, rbc	-	+	0	0	0
ChE, plasma	-	+	-	-	0
WBC	-	+	-	+	+
Hemoglobin	-	+	-	0	0
Hct	-	+	0	0	0
Cholesterol	+	+	+	0	0

1. Analysis of variance: $p < 0.05$

1. Analysis of variance: $p < 0.05$ or less

+ = significantly elevated; - = significantly lower; 0 = no difference
when compared with controls

**TABLE 4. Morbidity Study of Pesticide
Exposed and Control Participants**

Morbidity Indicator	Exposed	Control	Comparison ¹
Days lost from work	66%	59%	NSD
Hospitalized	20%	27%	NSD
Doctor-attended illness	73%	81%	NSD

¹ X² analysis; NSD = no significant difference

consistent with exposure history. While SGPT enzyme is elevated in all cohorts, another factor, namely organic solvents, should be considered. In addition to the typical pesticide solvents, members of the synthesizer and peripherally exposed groups are also exposed to ethyl and methyl alcohols which may participate in this enzyme's release. The acute cholinesterase inhibiting effect is noticeable in formulators and is generally of a transient nature. The significance of white blood cell, hemoglobin and hematocrit diminution in the formulators is not apparent.

Increased cholesterol among formulators, PCO's and farmers is significant. Speculation may lead one to consider that increased DDT burdens, known to accelerate the metabolism of estrogens through stimulation of microsomal enzymes, may thus diminish the inhibitory effects of estrogens on cholesterol and other lipid deposition in vessel walls.

Other Morbidity Indices

Table 4 shows no difference in the number of days lost from work due to illness, hospitalization, or physician visits between those exposed to pesticides and the control subjects.

Mortality

Three deaths occurred among the exposed population:

one each from stroke and lung cancer, and one burned in a fire. No deaths occurred in the smaller control group. Data from the deceased were not included in the morbidity reports included under medical history, physical exams, or morbidity index.

We do not think that significance can be attached to mortality occurring in this study because of the smallness of the cohort size. For example, in a study of this size, four deaths in the pesticide exposed group with no such events in the control group would have to occur, to demonstrate a meaningful difference in mortality.

Our findings agree somewhat with those of Wassermann's⁴ who concluded that, although no clinical findings or subjective complaints may be attributed to chlorinated hydrocarbon insecticide exposure, many subtle, subclinical or biologic findings indicate the influence of these chemicals on physiologic processes. While we admit that DDT and other pesticides may constitute one of the more important environmental burdens imposed upon the human race, we have thus far been unable to attribute an increased prevalence of acute or chronic disease to this burden.

SUMMARY

Four years of intensive study of 120 workers occupationally exposed to a wide spectrum of pesticides

indicate that these subjects have no greater incidence of morbidity or mortality than a control population. With minor exceptions, these results are consistent with those obtained by Hayes, et al.³ However, a much larger study would be necessary to find such slight differences in morbidity and mortality. Furthermore, our study has not dealt with populations probably at greatest risk, namely the fetus, children, pregnant females, and the elderly. Subtle biochemical differences of undetermined significance have been found. While this may be reassuring, our research suggests that pesticides, notably organochlorines and organophosphates, like certain other pollutants, may impose subclinical stresses on the human body, but no overt diseases have been uncovered.

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LIVING LABS THAT STUDY HOW PESTICIDES AFFECT MAN

PESTICIDES PROGRAM
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By Samuel W. Simmons, Ph.D.

In New Jersey, a worker in a pesticide chemicals factory reports after his shift to the plant clinic near Trenton for a thorough medical examination. In Texas, the pilot of a plane used for dusting agricultural crops with pesticides visits his doctor, and afterward, the physician reports his observations on the state of the pilot's health to the State Department of Health office in San Benito. In Mississippi, a farm laborer who lives near a cotton field regularly sprayed with pesticides reports to the University of Mississippi Medical Center at Jackson for intensive medical checkups. In Utah, a worker who applies pesticides in mosquito control work drops by the State Department of Health office in Salt Lake City for a medical going over.

These people have two things in common. They are regularly exposed by occupation or environment to pesticides with unusual frequency or in unusual amounts; for this reason, they have agreed to act as volunteer experimental subjects in a nationwide program aimed at bringing to light the effects this exposure may have on the various systems and organic processes of their bodies.

The Community Studies Pesticides Projects, collectively one of the most ambitious health observation programs ever undertaken on a countrywide scale, has been in operation since 1965. Since last July, the projects have operated under the Division of Community Studies of the FDA Bureau of Medicine's Office of Product Safety. The projects are carried out under Federal contract by State Health Departments or universities in 15 widely scattered areas or communities in the contiguous States and Hawaii.

Their objective: to collect and evaluate information aimed at finding whether and how exposure

to pesticides, as experienced in an occupation or in the environment, is affecting the health of Americans.

For the basic study in each community, the contractor keeps close tabs on the medical history of an average of 100 volunteers who, because of their occupations or their environment, are subject to greater exposure to pesticides than the population at large. They include workers in pesticide formulating plants; employees of plant nurseries; agricultural workers on farms, ranches, or orchards where pesticides are used heavily or often; pilots of aircraft that dust crops or ranges; pest control workers; or those who live in localities where pesticides may be expected to permeate the living area to a greater extent than would be found normally. In addition, a limited number of people from the general population known to have had only minimal exposure to pesticides are selected to serve as controls for comparison purposes.

These volunteers are given a complete annual physical and neurological examination by their physicians, and in some cases, the contractor carries out the medical examinations. Followup examinations are made periodically, and the results, including samples of urine, blood, and sputum, are analyzed in the contractor's laboratory for determination of any changes or effects. Fatty tissues or tissues from various organs are collected when available, as when a subject undergoes surgery, and are supplied to the laboratory.

The information emanating from the studies is evaluated medically and statistically and published in scientific journals. More comprehensive data is funneled on standardized forms to the Community Studies Division in Atlanta, where it will be processed for input into a

computer system being developed to see if medical, scientific, or statistical conclusions can be drawn that will have general significance or application. The Community Studies are supported with research in analytical chemistry, primate toxicology, quality control, and other services by the Perrine Primate Research Branch of the FDA Bureau of Science's Division of Pesticides (see color photo story) to assure consistent and uniform quality and high standards of laboratory work that will permit the findings in one community study to be evaluated on the same basis as those of another.

An important extension to the Federal Government's activities on the effects of pesticides on man and animals was the establishment by the Public Health Service of a toxicology laboratory at Savannah, Ga. In November 1964, the PHS Bureau of State Services established an Office of Pesticides to deal with a number of recommendations relating to public health that were made by the Life Sciences Panel of the President's Science Advisory Committee after its comprehensive study of the benefits and hazards of pesticides. The Office of Pesticides, which had been formed in Washington, D.C., was transferred in August 1966 to PHS's National Communicable Disease Center in Atlanta and consolidated with that Center's toxicological activities. The new organization was named the Pesticides Program, and in a PHS reorganization last July 1, the program was assigned as the Community Studies Pesticides Projects to the Division of Community Studies of the FDA Bureau of Medicine's Office of Product Safety.

Some of the project contractors are conducting one or more additional studies, usually by subcontract with other nonprofit medical or



Samuel W. Simmons, Ph.D., moved to FDA in 1968 as Chief of the Division of Community Studies. He was awarded the Gorgas Medal last year for past work in malaria control with the National Communicable Disease Center.

scientific groups, on special medical or health aspects that can be related to exposure to pesticides, to the effects of specific types of pesticides, or to special problems characteristic of one of the communities under study as related to crop, climate, temperature, working conditions, or other conditions worth considering.

The contractors put together a pesticide usage "profile" of their particular areas that includes the kinds and quantities of pesticides used, the amounts per acre, the time and location, the method of applying, the purposes of application, the strength at which the pesticide is applied, and whether it is applied from the air or on the ground. The laboratories analyze samples of the water and soil representative of the area, and determine if the area's food supply differs from the national average in pesticide residue content as published in FDA's continuing "market basket" statistics on pesticide residues in the national food supply.

The geographical areas involved were selected for the Community Studies because they are areas of high pesticide use; represent a cross-section of the climate, temperatures, and seasonal conditions to be found in various parts of the country; cover a variety of socioeconomic population levels ranging from poor crop workers to well-to-do farmers; or have eligible contractor groups available who are competent enough to take over the projects and carry them out.

The contractors and the Community Studies Division in examining their human subjects look not only for overt clinical illness or immediate changes, but also for the more subtle biochemical, functional, and behavioral changes, and for those that may occur on a more gradual or delayed basis.

The contractors also keep records on acute poisoning cases in their areas, investigating the kind of poison involved, how the incident happened and why. The physician attending such a case through prior arrangement supplies information on his findings and the contractor carries out diagnostic tests for organic, neurological, and physiological changes or effects. The Federal Aviation Administration keeps the contractors informed about crashes of aerial spray pilots, so they may carry out epidemiological studies and laboratory analyses to determine if pesticides are a contributing factor in these crashes. The acute poisoning cases provide valuable information not only on chemical, physiological, and behavioral effects caused by the chemicals, but also on the dose-and-effect relationship, the factors in the relationship of the victims to environments, and the methods being used to treat the various types of poisonings.

Poisonings are not uncommon in areas where intensive agriculture, horticulture, or pest control are practiced. The Florida study of Dade County disease and deaths revealed 133 cases of documented pesticide poisoning from 1964 through 1967 in a population of around one million people. Of these cases, attempted suicides accounted for 37, accidents for 67, and occupational poisoning for 25. Eight of the cases were homicides and two were unclassified. Of the 133 cases, 47 were fatalities.

Nationwide, the recorded death rate in 1965 from poisonings caused by all chemical solids, liquids, gases, and vapors was 5.0 per 100,000 people. The death rate associated with all pesticides in the United States for that year was reported at 1.0 per one million of population. Although there is no reliable data

on disease and illness due to pesticides, the estimate is that for every fatal poisoning there are 100 non-fatal cases. Since poisonings do continue to occur, the persons who study these cases can help the attending physician in determining the causative agent, the dose, the effects, the contributing factors, and ways to help eliminate this public health problem.

Their investigations of acute poisonings have given the contractors in the Community Studies an awareness of the chemical or clinical effects that merit further study. The Colorado project reports definite, if temporary, deficiencies in the memories, reaction times, visual and auditory responses, and muscular coordination of the victims of organophosphate poisoning during the first 3 days after poisoning. An electroencephalogram (EEG) may show definite changes; nerve conduction changes have been detected in patients with acute toxicity. Studies of blood coagulation after acute organophosphate poisoning have indicated a phase of abnormally rapid coagulation, then a phase of prolonged coagulation. Sugar in the urine and protein disorders of the blood are common after acute exposure.

The Florida project, analyzing clinical, chemical, and epidemiological aspects of 89 acute organophosphate poisoning cases, noted depression of the enzyme cholinesterase, glycosuria (sugar in urine), aminoaciduria, excretion of paratropenol, decreased reabsorption, decreased ability to acidify urine, and impaired ability of the kidney to concentrate urine.

These observations of acute poisoning victims provide valuable leads to the contractors for examining the subjects in the Community Studies who are occupationally exposed on a long-term basis. Their



investigation of poisoning epidemics also gives the contracting health officials a better understanding of the circumstances that led to an event and provides a basis for planning preventive measures.

In a 1967 poisoning epidemic in Tijuana, investigated by Mexican officials, over 500 people reportedly became ill and 16 died as a result of contamination by parathion of ingredients in bread. In 1967, in Qatar and Saudi Arabia, 1,874 people were hospitalized and 26 died from eating bread made from flour that had been stored in the holds of two ships under drums of endrin that leaked into the flour. Last July in Texas, 23 farmworkers became ill 2 hours after they entered a cotton field that had been sprayed the previous evening with parathion. In a recent homicide in Florida, seven children died from parathion poisoning. Three men were made ill last year from exposure to arsenic while repairing equipment in a New Jersey pesticide plant. A father in Mississippi brought home a concentrated organophosphate insecticide last year to combat flies, sprinkled it liberally around the house, and as a result, he and two of his children were severely poisoned. In 1967 in a small nursery for newborns in St. Louis, 20 babies developed an unusual illness and two died from exposure to sodium pentachlorophenate in a disinfectant that had been used by mistake in laundering their diapers.

These examples demonstrate something of the problem and the need for continuing investigation of poisoning epidemics so as to prevent similar misuse of such chemicals in the future.

The 15 Community Studies, although each is designated by the name of the State, do not usually cover the entire State. The typical pattern is a county or a small group of counties in a part of the State where a special problem is presented because of the kind of crop grown, the kind of pesticides used, the convenience to the contractor's laboratory and other facilities, or an urban area where pest control or pesticide manufacturing is centered.

New Jersey—State Department of Health, Trenton. A large number of pesticide products are manufactured in this heavily industrialized area.

South Carolina—Medical College of South Carolina, Charleston, and State Department of Health, Columbia. Study groups include pesticide plant employees, farmworkers, Corps of Engineers applicators of 2, 4-D, and family units living near waterways that receive herbicide treatment. The State Department of Health provides analytical chemistry facilities under subcontract.

Texas—State Department of Health, Hidalgo and Cameron Counties, around Brownsville and McAllen. Warm temperatures and modern irrigation make possible a

long growing season and large amounts of pesticides are applied from the air and the ground. A cooperative study with the Department of the Interior's Fish and Wildlife Service is seeking to determine the doses of pesticide man receives from eating certain game and fish taken in the area.

Louisiana—Louisiana State University Medical School and State Department of Health, New Orleans. Study groups include agricultural workers, family units, and pest control workers in the heavily treated cotton-growing and urban areas within the general vicinity of the city.

Mississippi—Mississippi State University, Greenville. Analytical facilities are at the MSU campus in Starkville. The University of Mississippi Medical Center, Jackson, under subcontract carries out intensive medical examination of exposed persons. The study groups are farm labor family units living near heavily sprayed cotton or other fields, staff members of MSU's Delta Experiment Station who work with either herbicides or insecticides, spray-plane pilots, and experimental farms run by pesticide manufacturers.

Florida—In two major parts. A statewide study by the State Department of Health is collecting death statistics on persons registered in the structural pest control industry for any 2 years during the period 1949-1965, and disease and death statistics on persons in structural pest control or lawn spraying for 2 or more years since July 1965, including State employees in mosquito control districts. In Dade County (Miami area), the University of Florida Medical School is studying acute poisonings among the general population, as well as studies of persons occupationally exposed and of the general population.

Arizona—University of Arizona,

Tucson, in Pima and Maricopa Counties. The study groups are sprayplane pilots, pest control workers, and farmworkers. In a special study in cooperation with the State Game and Fish Department, the project is comparing wildlife levels in uninhabited areas with those in heavily sprayed agricultural areas.

Iowa—Institute of Agricultural Medicine of University of Iowa College of Medicine, Iowa City. Under study is the nature of human exposure to pesticides and metabolites in tissues of domestic animals used for food; metabolism and storage of pesticide residues in domestic animals; effects of dose upon biochemical, physiologic, and pathologic changes; causal relationship of pesticide exposure to prolonged recovery time of surgical patients who have received the anesthetic succinylcholine, and of patients with blood dyscrasias. Iowa State University's Veterinary Diagnostic Laboratory, Ames, is under subcontract.

Michigan—State Department of Public Health, Lansing. Study groups are fruit growers, truck farmers, commercial sprayers, dairy farmers, and urban dwellers. Michigan State University is a subcontractor. A steering committee includes representatives of medical associations and health agencies, the State Departments of Agriculture and Health, and the State Water Resources Commission. This group helps in program planning.

Utah—State Department of Health, Salt Lake City. Study groups include area and urban mosquito spray workers, agricultural ground applicators of pesticides, and pesticide formulating plant workers.

Idaho—State Department of Health, Boise. Covers an agricultural area where large amounts of pesticides are used during a short growing season and where extensive

irrigation is used. Study groups include persons exposed environmentally and occupationally, along with a control group of persons who have had minimal exposure.

Washington—State Department of Health, Wenatchee. This is a center for growing apples and pears. Study groups include workers exposed to pesticides from spraying orchards. The project also is investigating the pharmacological effects of acute poisonings from accidents, suicides, and homicides, and is studying crashes of aircraft carrying pesticide sprays and health hazards involved in pesticide storage.

California—State Department of Public Health, Berkeley. Under study are blood dyscrasias in persons exposed to lindane and causal relationships between seasonal neonatal jaundice and the use of cotton defoliants in the Imperial Valley. One study is evaluating the changes in sputum cytology of persons exposed to pesticides. Study groups include State mosquito control workers.

Colorado—State Department of Health, Greeley (Weld County). This area raises crops of carrots and sugar beets and contains extensive cattle feeding lots. The project has concentrated on family units to determine the source of family exposure to pesticides in house dust, soil, food, water, and drift from treated fields. The units are under continuous medical and biochemical surveillance. Other study groups include crews of aerial spray companies and, under subcontract with the University of Denver Medical Center, Denver, industry personnel in pesticide manufacturing and processing.

Hawaii—University of Hawaii in cooperation with the National Institutes of Health Hawaiian Cardiovascular Study and the State Depart-

ment of Health. The study group includes thousands of men of Japanese ancestry on the Island of Oahu, with particular attention to cardiovascular disease, asthma, bronchitis, and sinusitis. Hawaii's tropical climate makes possible year-round agricultural work. Termites are a problem here. Pesticides are heavily used for both crop treatment and termite control.

Although the Community Studies Pesticides Projects are learning much about pesticides and their effects on man and animals and the environment, there is no end in sight for the projects so long as pesticides continue to be used by man in his efforts to control pests that threaten his comfort, his health, and the food supply. Although some aspects of the studies may be attenuated or terminated when the information they seek is complete or conclusive, many problems will remain and new ones will arise, among them those created by the many new pesticide compounds and formulations put on the market each year.

The pollution of the environment by a growing number of synthetic and natural chemical agents presents a potentially serious challenge to the health of present and future generations of both man and animals. The Community Studies thus are contributing importantly to the research efforts in pesticides that are essential to maintaining the well-being of our society: they are enlisted in a wide and comprehensive undertaking to help make some order and sense out of a major problem to health and to find ways to successfully cope with it in the interest of the public welfare. The data that they gather and evaluate will provide a better understanding of the risks versus the benefits of using pesticides as part of the larger pattern of our continued existence and prosperity.

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PESTICIDES PROGRAM
 National Communicable
 Disease Center

New Leads in Pesticide Health Research



Important areas for future research on long-term human health effects from exposure to pesticides have been identified by investigators working under Public Health Service Office of Pesticides contracts.

Among meaningful new leads to knowledge of relatively little understood pesticide-health relationships are findings by Office of Pesticides community researchers in Dade County, Florida, which indicate that persons regularly and highly exposed to parathion risk kidney malfunction.

Preliminary evidence of aminoacidemia has been found in adults with a history of high and/or long exposure to pesticides. Levels of amino acids found in the urine indicate an enzymatic defect in protein metabolism. Initial evidence indicates that this is an irreversible defect. The pattern of aminoacidemia found does not fit typical amino acid defects as currently recognized in man. In addition, below normal phosphorus reabsorption indices were determined for 20% of 34 persons under study. Some were also shown to be unable to concentrate urine with normal efficiency as demonstrated by tubular water concentration measurements and to have below normal acid base regulation.

The significance of placental transmission of pesticides in humans, also shown by the Florida investigators, remains to be determined by further research. Initial evidence has shown chlorinated hydrocarbon pesticides in stillborn fetuses to equal closely that of the mother. The importance of this finding is that from the earliest embryonic state the human fetus re-

ceives an adult level of exposure. Other data suggest that pesticide levels decline rapidly after birth and gradually rebuild over a period of several years.

Aberrations in behavior and psychological responses among persons with prolonged exposures to pesticides, particularly of the organic phosphate type, have been found by community researchers in Colorado. A consistent pattern of abnormal electroencephalographic changes has been determined. These changes do not fit typical space-occupying lesion patterns, nor are they consistent with known abnormal metabolic states. Possible association with personality defects is strongly suggested.

Public Health Service researchers recently developed a promising and rapid test for detecting insecticide concentrations in blood that is less complex than the presently used fat biopsy method. However, further experimentation must be conducted before it can replace tissue analyses. Eventually it may be a useful tool to determine pesticide levels in large, epidemiologically significant numbers of people.

The new Pesticides Research Laboratory of the Public Health Service is reaching full-scale operations under Office of Pesticides management with emphasis on long-term health effects of pesticides.

Clearer understanding of possible relationships between pesticides and chronic human ailments is of major importance to the Office of Pesticides for achievement of its mission to improve protection of public health from modern synthetic pesticides.

Importantes áreas para investigación en el futuro sobre la acción a término prolongado de los efectos sobre la salud humana de los pesti-

cidas han sido identificadas por los investigadores trabajando por contrato con el Public Health Office.

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HEALTH HAZARDS IN THE USE OF PESTICIDES

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In studying the potential health hazards associated with the use of pesticides, three segments of the population should be considered. These segments include:

1. The formulator or sprayman who mixes and/or sprays the chemicals and has a relatively high degree of exposure.
2. The so-called "innocent by-stander" who has no intentional exposure but who may be inadvertently exposed when dust or spray drifts onto his home during application to adjacent fields or orchards. The child who innocently plays with a supposedly empty insecticide container, or who eats or drinks a pesticide from an unlabelled bottle, also may be considered in this category.
3. The general population, all of whom have some degree of exposure to pesticides residue in their daily diet. Studies carried out at our laboratories have attempted to evaluate the hazard to each of these population groups from pesticide usage.

Exposure of Spraymen

Batchelor and Walker (1954) measured the exposure which spraymen receive during orchard spraying with parathion. This work involved the assay of dermal exposure by attaching absorbent patches on the skin of workers during actual spray operations. Respiratory exposure was measured by analyzing the filter pads from each worker's respirator, and by determining the parathion content of air samples taken near the breathing zone of the operator. The results of these tests have indicated that the dermal route is much more important than the respiratory route, not only with respect to total exposure but also with reference to the fractional part of the toxic dose which is potentially absorbed.

It appears from these studies that the exposure of spray personnel to parathion approaches the toxic level as calculated by extrapolation from data on toxicity studies in laboratory animals. The explanation for the fact that this degree of exposure is, to a large extent, innocuous may be related to the timing of exposure. Thus, the spray personnel receive their exposure spread out over a period of 8 hours or more while the laboratory rats were given a single, acute dermal dose of the poison.

In this connection, Rothe et al. (in preparation) have shown that rats can withstand more than an LD₅₀ of parathion daily for many days without significant injury provided the material is given in their food so that the dose is received gradually rather than instantaneously as in the case of a single, acute dose given by stomach tube.

Batchelor, Walker, and Elliott (1956) measured the exposure of orchard sprayers to dinitroorthocresol during its use as a thinning spray for apples.

In Europe there have been a number of illnesses and some deaths among spray operators applying this material. However, the studies of exposure pads and of blood and urine levels of the compound which were done in the State of Washington indicated that no significant hazard was involved in the use in the recommended manner of DNOC for thinning blossoms.

During the 1958 spray season there occurred a rather large number of illnesses allegedly due to pesticides in central Washington. These cases included two fatalities and approximately 100 illnesses ranging in severity from very mild (with no time lost from work) to serious (involving several days of hospitalization). In 71 of the 100 cases, it was considered that an etiology of pesticide poisoning was established by exposure history, clinical symptoms, and/or laboratory tests. Most of the poisoning cases involved parathion, the most widely used of the more toxic pesticides in this area. However, demeton (Systox) and Phosdrin were also involved. No cases of chlorinated hydrocarbon poisoning were seen.

Several factors may have been involved in the higher incidence of poisoning observed during 1958. These factors include:

1. Several years of usage with no adverse effects may have caused some workers to become lax in their observance of safety precautions.
2. Greater insect infestation and the development of some resistant strains necessitated a greater than normal usage of insecticides.
3. The summer of 1958 was one of the hottest on record in this area.

It appears that poisoning occurs more often in the hotter weather. This may be because people spray more often and wear less protective clothing in hot weather. Increased skin absorption and greater volatilization of the toxicants should also be considered. The incidence of poisoning was somewhat lower during 1959. The factors mentioned above which contributed to an increase in poisoning in 1958 were all functioning in reversed direction in 1959, including greater general awareness of toxic hazard, less insect infestation, and lower average temperatures.

Foliage Residues

Another facet of the exposure of orchard workers involves residue on foliage. The ability of parathion residues on foliage to poison crop workers has not been generally appreciated. Our laboratory has investigated eleven instances of parathion residue poisoning in crop workers (Quinby and Lemmon, 1958). Etiology was confirmed by a lowered blood cholinesterase level (seven instances) and by improvement following atropine administration (nine instances). Of a total of 142 persons exposed, 75 became ill.

These mild poisonings have occurred in workers thinning, picking, or irrigating crops of apples, pears, grapes, oranges, and hops treated with 1 or more pounds of parathion per acre. Several of the known instances of poisoning involved exposure to foliage or fruit sprayed not more than 2 days earlier. However, contact with pear trees, grape vines, and orange trees caused poisoning as much as 12, 33 and 34 days, respectively, after application. There were several outbreaks of residue poisoning among citrus pickers in California during 1959. Studies will be carried out during the 1960 season in an attempt to learn the factors involved in the etiology of residue poisoning.

The hazard to residents from spraying adjacent orchards has been evaluated by Sumerford and his coworkers (1953) in extensive studies carried out in 1951 and by Hayes and colleagues (1957) in studies done in 1952 and 1953. This work involved study of blood cholinesterase levels and incidence of illness among groups of persons with different degrees of exposure to organic phosphorus insecticides.

Blood cholinesterase values were found to be depressed during the period of exposure for those groups (including formulators and spraymen) having definite exposure. No change in blood cholinesterase during the spray season was seen in the groups (including residents in or near orchards) with little or no exposure. Illness suggestive of poisoning was increased in the definitely exposed groups during the period of their exposure. Illness resembling mild poisoning was not significantly more common in persons (including those residing in or adjacent to orchards) living in an agricultural community who had no occupational or gross accidental exposure than it was in persons living in a nonagricultural area, where insecticides were not used.

Recent advances in this area of study have included the development of a new and more sensitive procedure for the measurement of exposure to parathion. This procedure involves the assay of urinary excretion of a parathion metabolite, p-nitrophenol (Elliott *et al.*, in press). The excretion of p-nitrophenol has been found to be a more sensitive measure of exposure to parathion than is blood cholinesterase activity (Arterberry *et al.*, in preparation).

A study was carried out in 1958 using this more sensitive method to determine the parathion exposure of residents in or adjacent to orchards during spray operations. The average p-nitrophenol excretion level of the orchard residents group was too low to be significant. Only one individual in this group had one sample which contained a significant quantity of p-nitrophenol. Workers with higher degrees of parathion exposure generally excreted easily measurable quantities of p-nitrophenol, even though many showed no effect of the exposure on their blood cholinesterase activity level. Thus, this more sensitive measure of exposure essentially confirms earlier results with blood cholinesterase tests and symptomatology. All three types of tests indicate that the exposure of orchard residents during spraying is insignificant.

Disposing of Containers

Each year, tragic, preventable poisonings occur when children obtain food containers filled with insecticide or get hold of "empty" insecticide containers. Although empty insecticide bags are easily destroyed by burning, the disposal of empty cans presents somewhat more of a problem. Recent work has shown that empty parathion cans can be decontaminated by the use of solutions of lime or lye. More practically, however, simply washing with water was also found to be quite effective. As an average, less than 1 per cent of the residual parathion was left after two rinsings of the 5-gallon cans with 1 gallon of water.

The primary pharmacologic action of the toxic organic phosphorus compounds is their ability to inactivate the enzyme, cholinesterase, with a resultant build-up of acetyl choline, giving rise to symptoms of over-stimulation of the parasympathetic nervous system. Atropine is a pharmacologic antagonist of acetyl choline and has proved to be an effective antidote in cases of poisoning by organic phosphorus compounds. In severe cases, artificial respiration may

be life-saving, since the usual cause of death is respiratory failure. Some progress has been made recently toward finding a "true" antidote for these compounds. The hydroxamic acids appear to possess the property of splitting, both in vitro and in vivo, the combination of the organic phosphorus molecule with cholinesterase, thus reversing the enzyme inhibition.

Two members of this antidotal group which have received considerable notice are known as 2-PAM and DAM. A supply of 2-PAM is on hand at our laboratory in Wenatchee as well as at our other stations in Savannah, Georgia and Phoenix, Arizona. We will be glad to make this drug available to physicians in the event of need.

The Phoenix laboratory has recently reported the recovery of a severe poisoning case following the administration of 2-PAM (Funckes, 1959). The patient had been poisoned with parathion and even after administration of atropine his prognosis was considered poor. The patient showed dramatic improvement 10 minutes after administration of the drug and was dismissed from the hospital 5 days later.

The hazard to the ultimate consumer of a very few pesticide residues in foods has also been evaluated. Thus, Upholt and his coworkers (1954) studied blood cholinesterase levels and general health status of volunteers who ate apples and peaches which had been sprayed with Systox. No volunteer showed cholinesterase diminution as a result of this diet and none reported illness attributable thereto.

DDT in Foods

Walker et al. (1954) determined the DDT and DDE content of a series of restaurant and institutional meals. Every meal tested contained some DDT. However, not all the items of food contained DDT. The DDT content was generally proportional to the animal fat content of the foods. On the basis of this work, it was calculated that the average daily dietary intake of DDT would be 184 micrograms. Extensive studies on experimental animals, carried out by our laboratories and by numerous other groups in this country and abroad, indicate that this dietary level of DDT would not be harmful. However, as has been pointed out so well by Seevers (1954) although experiments with animals may provide a valuable guide, the only way in which one can definitely be sure of the toxicity of a chemical to man is through studies on man.

To clarify the question of hazard to man, a study has been carried out involving the administration of small daily doses of DDT to human volunteers for periods up to 2 years (Hayes, et al., 1955). The volunteers were divided into three dosage groups. These groups received 0, 3.5, and 35 mg. DDT per man per day, respectively. The two later dosage levels correspond, respectively, to about 20 and 200 times the 184 microgram figure cited above which is the calculated amount of DDT the average person in this country ingests in his daily diet. During the 2 years of this study, no volunteer complained of any symptoms or showed, by the tests used, any sign of illness that did not have an easily recognized cause clearly unrelated to exposure to DDT. DDT and DDE accumulated in the body fat and DDA was excreted in the urine. In an additional, long-term study now underway the length of time required to dissipate stored DDT and DDE from body fat will be determined.

Since transportation is included in the theme of this conference, I am sure you will be interested in two incidents in which contamination of food stuffs

with a pesticide during shipment resulted in a number of cases of poisoning. Neither of these incidents took place in this country.

Over 100 deaths occurred in India during the spring of 1958 from eating food accidentally contaminated with a pesticide during shipment (Anantaswamy, et al., 1957). The board of inquiry reported that there has been faulty storage of parathion in polyethylene containers, failure to pack these containers with absorbent materials, and failure to provide adequate labelling. The board found that there had been a deliberate false description of the consignment in the waybills and invoices covering the shipment of the pesticide, since the product had been classified as "harmless."

In Britain in 1956, forty-nine people became ill after eating bread made from endrine-contaminated flour. (Davies and Lewis 1956.) This flour had become contaminated during shipment in a railway car in which endrin had previously been spilled. There were no fatalities in this latter group of cases.

Summary

In summary, our laboratories have carried out studies designed to evaluate the potential health hazard of pesticides to the three segments of the population having exposure. The formulator or sprayman group on the average has the greatest potential exposure. When working with hazardous materials, these men run the risk of illness or death if they do not adhere closely to recommended safety precautions. Potential exposure is very much less for persons having only environmental exposure or for the consumers of pesticide-treated foodstuffs.

All our studies indicate that all pesticides, even the most hazardous, can be used with safety provided that recommended precautions are followed.

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Exposure of Formulating Plant Workers to DDT

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Potential dermal and respiratory exposure of workers to DDT in two formulating plants showed higher exposure where observations indicated poor housekeeping and inadequate ventilation. Exposure calculations indicated that if workers did not wear recommended protective gear the potential exposure would be $2\frac{1}{2}$ to 10 times greater than when wearing recommended gear. Highest estimated potential exposure was at a bagging station where the mean dermal value was calculated to be 524.5 mg/hr and the mean respiratory exposure, 14.1 mg/hr. Relatively low levels of DDA in urine of men in work situations of higher potential exposure indicate that the protective gear worn by workers was effective and probably reflects inefficient dermal absorption of DDT. Urinary excretion of DDA over a five-day period indicated that excretory levels of the metabolite correlated well with exposure periods.

SEVERAL previous studies of exposure of workers to DDT in manufacturing and formulating plants have been carried out in this and other laboratories.¹⁻⁵ In these studies, indirect methods for measurement of exposure were employed which involved determination of levels of DDT and DDT-derived material in blood, fat and other tissues, and excretion of DDA in the urine as an indication of exposure of workers to

DDT. The measurements reflect DDT absorption into the body. The workers studied had varying degrees of protection from exposure, ranging from the use of very little protective clothing to relatively adequate protection, including the wearing of respirators.

Ortelee,¹ in an exposure study of workers in manufacturing and formulating plants, estimated DDT absorption by comparing urinary DDA concentrations with those obtained in a study⁶ of human volunteers on known daily oral dosages of technical DDT. Estimation of potential exposure was classed as "slight," "moderate," or "heavy," based on observations of the men at their jobs and also on an estimate by the men and by their superiors as to the degree of their exposure. In another study of exposure of workers in manufacturing and formulating plants, Laws et al² estimated that the average daily intake of DDT by 20 men with high occupational exposure was 17.5 to 18 mg per man per day as compared with an average of 0.04 mg per man per day for the general population. These figures were based on storage of DDT in fat and excretion of DDA in urine.

Edmundson et al^{4,5} also utilized indirect methods of measurement of exposure of pesticide formulators to DDT by determining levels of DDT and DDE in blood and of DDA in the urine, as did Durham et al³ in determining DDA excretion levels in workers, including those exposed in formulating plants.

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Although direct methods for measurement of potential exposure to DDT have been carried out for workers applying pesticides,⁷⁻¹⁰ we are not aware of any studies of direct measurements of potential exposure of formulating plant workers to DDT. The present studies, using direct methods, were conducted to determine the amount of impingement of DDT on body surfaces and the amount of DDT entrapped on respirator pads during given periods of work in formulating plants. The values obtained were used to estimate the amount of DDT the workers were subjected to as potential exposure when using certain recommended protective gear or clothing, and also to estimate the maximum potential exposure of workers when no special protective clothing or devices are used. DDA excretion was determined in several instances for correlation with potential exposure data.

Materials and Methods

The study was conducted in two plants formulating 50% water-wettable DDT powder. In order to determine the potential exposure in different work situations, exposure pad studies were carried out on (1) the worker who inserted the proper proportions of ingredients into the formulating machine ("mixer"), (2) the worker who filled bags with pesticide at the filler spout ("bagger"), (3) the worker who operated a machine to sew tops of bags closed ("sewer"), and (4) the worker who packed filled bags into cartons ready for shipment ("packer"). Exposure tests were carried out during work periods lasting from 30 minutes to 1 hour.

The amount of DDT to which a worker potentially would be subjected during work activities was estimated by the techniques and procedures described by Durham and Wolfe.¹¹ Dermal contamination was measured primarily by attaching layered-gauze absorbent pads to various parts of the worker's body or clothing and allowing them to be exposed during a timed period of work. Respiratory exposure was estimated from the contamination of special filter pads used in place of the usual outer absorbent filter pads which cover the filter cartridges of the respirators worn by the subjects. The filter pads were covered with plastic funnels modified to a specific aperture size to reproduce as nearly as possible the aerodynamics of air flow through the nostrils. The funnels also prevented direct impingement of particles

onto the pad except for those carried through the apertures by respiratory action. This technique renders it unnecessary to measure total air volume, because all inhaled air passes through the filter pads.

Respirator and dermal exposure pads were extracted with benzene in a Soxhlet apparatus, and samples were analyzed for DDT by electron-capture gas-liquid chromatography. Values obtained were used to calculate the milligrams of potential exposure per man per hour of work. The percent of the toxic dose to which workers were potentially exposed was calculated by the procedure described by Durham and Wolfe,¹¹ based on comparison between the dermal and respiratory exposure values determined in the present study and animal toxicity figures published by Gaines.¹²

Single urine samples were collected from 17 different workers following extended DDT formulation operations in the plants. In addition, two workers who seemed to be receiving the heaviest exposure collected complete 24-hour specimens of urine for a period of five days so that the rate of DDA excretion could be determined. A total of 171 urine samples were analyzed for DDA content by the method of Cueto et al.¹³ The DDA was expressed as DDT equivalent (actual DDA $\times$ 1.24).

Results and Comment

Potential Dermal and Respiratory Exposure.—Table 1 and 2 present exposure values for work stations in two formulating plants. The calculations in Table 1 are not based on the actual protective gear worn but on the use of minimum protection (no respirator, shirt with short sleeves, open collar, no hat, no gloves; it was assumed that the clothing worn gave complete protection of areas covered). The purpose of this was to arrive at values that might reflect the maximum potential exposure that could occur in different work situations where proper protective gear was not utilized. Table 2 shows values for the same workers but calculations were based on actual protective gear worn by the different individuals.

In plant A, no values were obtained for the mixer, and in plant B no values were obtained for the packer; no sewer was employed in plant B because of the use of a bag sealing machine. However, it is believed that the work stations studied were a fair representation of the plant working areas which have the greatest potential for pesti-

cide contamination. Observations indicated that the potential exposure would be much higher in plant A than in plant B, not only because the ventilation system was obviously inadequate in plant A but also because the presence of pesticide dust on the equipment, floor, and building structural members indicated a laxity in plant housekeeping. These observations were confirmed by the results.

As can be seen in Table 1, the highest potential exposure values were for plant A. An example of the difference in potential exposure between the two formulating plants can be seen in values for the workman (bagger) who filled 4- and 5-lb bags with pesticide. The bagger in plant A would have been subjected to a potential dermal exposure of from 95.0 to 992.9 mg/hr, with a mean of 524.5 mg/hr of DDT had he not worn recommended protective gear. This is approximately 17 times more potential dermal exposure than for the bagger in plant B (range, 24.6 to 34.0 mg/hr; mean, 31.2), where more adequate ventilation and better housekeeping practices were in force. The potential respiratory exposure value obtained for this work position in plant A was from 4.20 to 33.80 mg/hr, with a mean of 14.11 mg/hr, or approximately 88 times more than the 0.14 to 0.19 mg/hr (mean, 0.16 mg/hr) in plant B. Such great variation in exposure conditions in formulating plants is not uncommon.

Some differences in potential exposure can be noted for the different work positions. In plant A, the worker at the 4- and 5-lb bagging station was subjected to the highest exposure, followed by the sewer, the bagger at the 50-lb bagging station, and then the packer. Inadequate ventilation at the filler spout appeared to contribute most importantly to exposure of the worker who filled the 4- and 5-lb bags. Occasionally, malfunction of the filler spout mechanism resulted in gross contamination of the worker. The authors have observed that these two problems are not uncommon in pesticide formulating plants. During one work period, malfunction of the filler spout was responsible for the very high respiratory value of 33.8 mg/hr for the bagger. The sewer station was located only 5 feet from the bagging operation, and it was observed

that contamination from the bagging station was reaching the sewing machine area. The packer who packed bags of pesticide into cardboard shipping cartons was located approximately 15 feet from the bagging station and received very little contamination from that area. At the packing station, the main exposure appeared to be from small amounts of water-wettable DDT powder being blown from inside the carton onto the face and upper body area as the worker pressed the filled bags tightly in place.

The 50-lb bagging station was located in a separate area and required no sewing or packing operation. At this location, much of the exposure of workers appeared to be from contact with dry pesticide that had been blown into the air as filled bags were removed from the filler spout and again when the flap over the filler hole of the bag was being closed by folding.

If all the DDT from the potential dermal and respiratory exposure to which a worker might be subjected when wearing a minimum of protective gear (as shown in Table 1) were completely absorbed, the calculated percent of toxic dose per hour of exposure (highest value of 0.76% for the bagger in plant A) is not particularly high as far as potential for producing acute toxic effects is concerned. However, possible long-term effects of excess absorption and storage in the body resulting from continued high exposure to DDT should be a subject of greater concern than the more remote possibility of acute toxic effects to workers. Thus, the relatively high potential dermal and respiratory exposure to this compound in formulating plants, even though DDT is of much lower toxicity to warm-blooded animals than many other compounds in common use, emphasizes the importance of following safety precautions to prevent excess exposure.

Exposure values in Table 2 are presented as an estimation of potential exposure in the different work stations, taking into account the protective clothing and respirators actually worn by the workers. Workers in both formulating plants wore rubber boots, cap, respirator, cloth coveralls with long sleeves but with top button at neck open, and rubber gauntlet gloves, which provided some protection at the wrist area not covered by

Table 1.—Potential Exposure of Formulating Plant Workers to DDT, Based on Minimum Protection*

Work Position†	Size of Bags	No. of Work Periods Studied	Exposure			
				Dermal (mg/man/hr)	Respiratory (mg/man/hr)	Total (Percent Toxic Dose per Hour)
Plant A						
Bagger	4 & 5 lb	4	Range Mean	95.0-992.9 524.5	4.20-33.80 14.11	0.08-0.76 0.39
Bagger	50 lb	4	Range Mean	105.8-226.5 153.5	3.26-11.80 6.07	0.09-0.20 0.12
Sewer	4 & 5 lb	4	Range Mean	32.6-706.8 498.0	0.42-9.05 4.86	0.03-0.45 0.31
Packer	4 & 5 lb	4	Range Mean	69.2-146.7 98.5	0.91-7.22 4.00	0.005-0.13 0.08
Plant B						
Bagger	4 lb	5	Range Mean	24.6-34.0 31.2	0.14-0.19 0.16	0.015-0.020 0.019
Mixer	4 lb	5	Range Mean	13.3-44.7 32.7	0.11-0.61 0.26	0.014-0.030 0.020

* Minimum protection: no respirator, shirt with short sleeves and open collar, no hat or protective gloves, leather shoes; it is assumed that clothing worn gave complete protection of areas covered.

† Bagger, worker who fills bags with pesticide at the filler spout; sewer, worker who operates a machine to sew tops of bags closed; packer, worker who packs filled bags into cartons ready for shipment; mixer, worker who inserts the proper proportions of ingredients into the formulation machine.

Table 2.—Potential Exposure of Formulating Plant Workers to DDT, Based on the Wearing of Certain Protective Clothing and Devices*

Work Position†	Size of Bags	No. of Work Periods Studied	Exposure			
				Dermal (mg/man/hr)	Respiratory (mg/man/hr)	Total (Percent Toxic Dose per Hour)
Plant A						
Bagger	4 & 5 lb	4	Range Mean	26.4-124.4 72.7	0.083-0.676 0.282	0.015-0.075 0.043
Bagger	50 lb	4	Range Mean	24.3-87.5 43.5	0.065-0.236 0.122	0.014-0.051 0.025
Sewer	4 & 5 lb	4	Range Mean	10.7-223.2 71.2	0.008-0.181 0.097	0.006-0.130 0.040
Packer	4 & 5 lb	4	Range Mean	15.2-32.5 26.2	0.018-0.144 0.080	0.009-0.019 0.015
Plant B						
Bagger	4 lb	5	Range Mean	7.8-19.6 14.3	0.002-0.004 0.003	0.004-0.011 0.008
Mixer	4 lb	5	Range Mean	4.2-18.2 12.9	0.003-0.012 0.005	0.002-0.010 0.007

* Coveralls with long sleeves and open collar, cap, rubber gauntlet gloves; it is assumed that the clothing worn gave complete protection of areas covered and respirators worn provided 98% respiratory protection.

† Bagger, worker who fills bags with pesticide at the filler spout; sewer, worker who operates a machine to sew tops of bags closed; packer, worker who packs filled bags into cartons ready for shipment; mixer, worker who inserts the proper proportions of ingredients into the formulation machine.

Table 3.—Levels of DDA in Urine of Workers Following Exposure to DDT in Formulating Plants on Two Different Days

	Worker No.	DDA Levels Expressed as DDT Equivalent (ppm)	
		Day 1	Day 2
Plant A: areas of greatest contamination*			
	1	0.04	0.10
	2	0.68	...
	3	0.18	0.18
	4	0.57	0.14
	5	0.50	0.50
	6	0.16	0.14
	7	0.27	0.38
	8	0.26	0.27
Plant A: areas of less contamination†			
	9	0.04	0.02
	10	0.14	0.12
	11	...	0.07
	12	0.02	0.02
	13	...	0.35
	14	0.40	0.17
	15	...	0.61
Plant B: areas of greatest contamination*			
	16	0.08	0.07
	17	0.06	0.04

* The general areas of bagging, sewing, mixing, or packing operations.

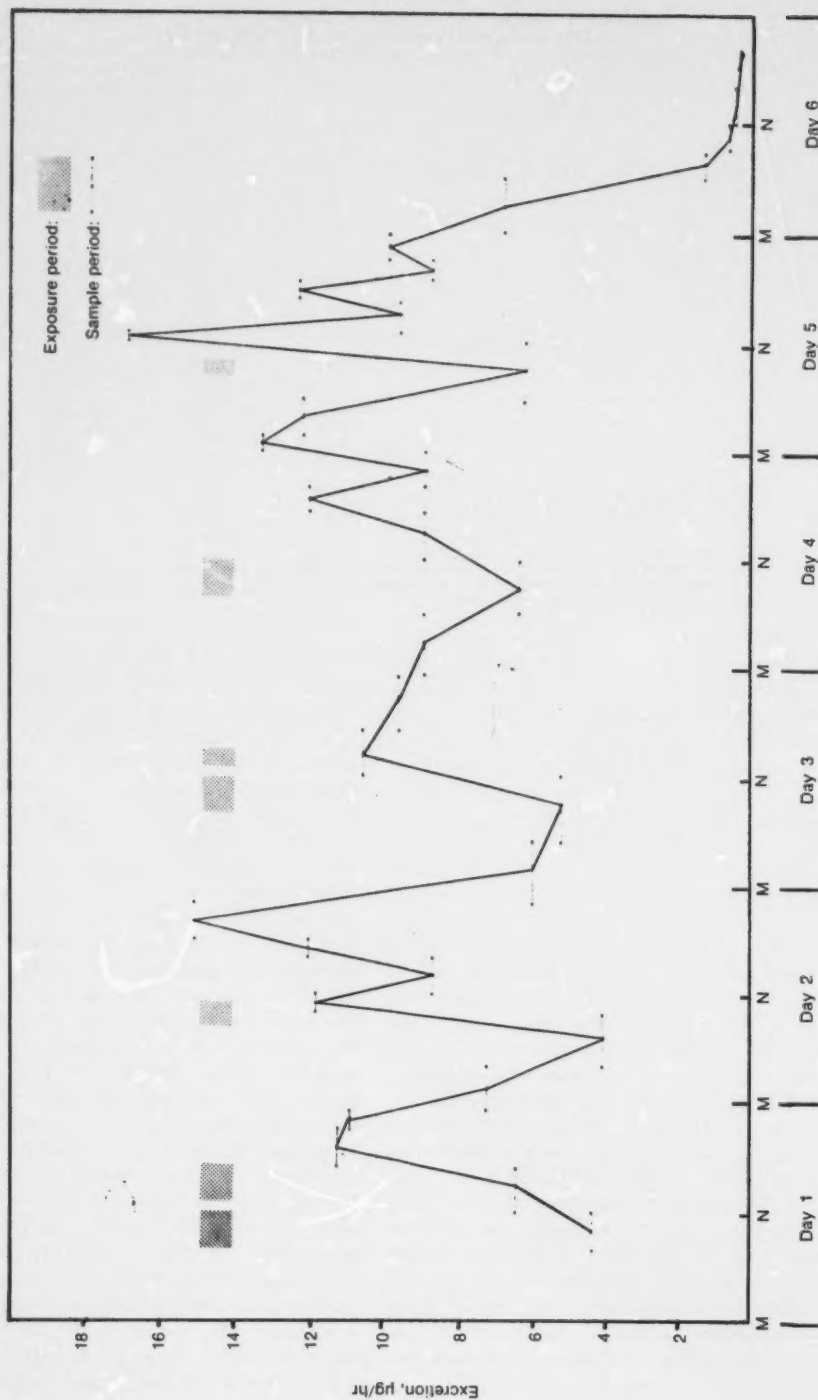
† Areas of less contamination such as storage, shipping, or other areas. Workers 13 and 14 were foremen who moved to all areas.

the sleeve. In plant A, the caps worn were the type with a bill at the front; the bill was considered to give some protection from downward-moving particles in the face-front area but very little protection on other face-neck areas. In plant B, the caps worn were the beanie type with no bill, and provided protection only for the top of the head. Also, rubber aprons were worn in plant B. Calculations of potential exposure were based on the assumptions that the clothing worn gave complete protection of the body areas covered and that the respirators fit tightly enough to allow passage of no more than 2% of the potential respiratory exposure. Exposure values were calculated for each worker, taking into account the estimated percentage of skin area actually exposed.

Data in Table 2 indicate that wearing additional protective gear reduces the potential exposure considerably. By comparing the mean values for percent of toxic dose received per hour with those calculated in Table 1, it can be seen that had the workers not worn the recommended added protective clothing and respirators they would have been subjected to approximately five to ten times more DDT in plant A and approximately 2½ to 3 times more in plant B.

Unfortunately, the wearing of clothing which provides only minimum protection and nonuse of a respirator are not particularly uncommon in formulating plants where compounds of relatively low toxicity, including DDT, are being handled. Ortelée,¹ in his study of workers in manufacturing or formulating plants, observed that in most cases no special protective clothing or respirators were used by the men while working with DDT. Thus, it is not surprising that his calculations indicated that the workers had absorbed an average of about 200 times as much DDT as that absorbed by the general population from dietary sources. Our observations in formulating plants indicate that, when workers are at the bagging station and not wearing respirators, it is almost impossible for them to avoid inhaling large quantities of the compound which is sometimes obviously present in high concentrations near the breathing zone. When 50% water-wettable DDT powder is involved, the intake may be quite significant. In view of the occurrence of occasional potential respiratory exposure as high as 33.8 mg/hr, as reported in the present study, or even much less than that amount, the 647 ppm of DDT-derived material found in the fat of a

Excretion of DDA (DDT equivalent) by a formulating plant worker following several exposure periods. Sample period represents interval covered by collection of a voiding of urine (total number of hours per voided specimen).



formulating plant worker by Laws et al² is not difficult to comprehend.

Urinary Excretion of DDA.—Levels of the metabolite DDA (expressed as DDT equivalent) found in urine of workers are shown in Table 3. Single urine samples were collected on two different days from men in different work areas. DDA in the urine of workers who spent most of their work day in the bagging, sewing, mixing, or packing areas generally was higher than that found in the urine of workers spending more time in areas of less DDT contamination. This indicates that even though workers in the areas of higher contamination wore more protective gear they absorbed more DDT than the other workers. The lack of high values for the two workers in plant B reflects the lower estimated potential dermal and respiratory exposure for these individuals. It was not possible to establish definite excretion values for specific work stations because of the occasional shifting of personnel from one work position to another.

Workmen listed as numbers 13 and 14 were foremen and moved to all areas of the plant. The level of DDA in urine of these two individuals was in the range of that of workers in areas of greatest contamination, probably because the foremen did not wear respirators or any added protective clothing when spending limited periods of time in such areas.

In addition to single urine specimens on most workers, two workers who appeared to be receiving the heaviest exposure collected complete 24-hour urine specimens for a period of approximately five days. Each voiding was collected in a separate container so that the rate of DDA excretion could be determined. The accompanying Figure shows excretion of DDA (as DDT equivalent) for one of these subjects. Although this individual excreted slightly more than the other worker, the excretion levels in relation to exposure were similar; therefore, the curve showing amount excreted per hour is given for only the subject having the greatest excretion. This worker served as a packer during portions of the first and third days, and as a bagger during portions of the second, fourth, and fifth days. On the sixth day, Saturday, the subject did not work; and, thus, no exposure to DDT was involved.

The excretion levels correlated quite well with exposure. Following each exposure period, the excretory level of DDA increased and reached a maximum, on the average, 10.6 hours after exposure began. This value agrees closely with the maximum excretion time of 10.1 hours found by Wolfe et al¹⁴ for pesticide applicators exposed to liquid DDT sprays in the field, and is near the 14 hours reported by Edmundson et al⁵ for workers exposed to DDT in formulating plants. The mean maximum excretion rate for the five days was 12.6 $\mu\text{g/hr}$, with a range of 6.5 μg to 16.9 $\mu\text{g/hr}$. The total excretion of DDA during the period was only 998.9 μg .

As can be seen in the Figure, DDA excretion fell to a very low level during the sixth day, which was not a work day. The subject reported that he remained relatively inactive inside his dwelling most of the day. Thus, he was not only less active but he was also not subjected to the higher outside temperatures. These factors, in addition to the termination of DDT exposure, may have contributed to the marked rate of decrease in excretion.

Although at the time of this writing the future use of DDT appears somewhat uncertain, it seems proper to add to the record of this compound its potential for dermal and respiratory contamination of workers in certain formulating plants. The finding of relatively low levels of DDA excreted, as compared with the relatively high potential exposure, indicates that the protective gear used by the workers was effective. If protective gear had not been worn there undoubtedly would have been more excretion of DDA, as was found by Ortelee¹ and Laws et al² in their studies of formulating plant workers. Even though all but the high values for DDA content of urine of workers in the present study fall within the range of levels excreted by the general population reported by Durham et al,³ correlation of excretion levels with exposure, seen in the Figure, is evidence that increased excretion was due to exposure in the formulating plant.

The finding of relatively high values for potential exposure to DDT and relatively low DDA excretion in urine also indicates that there was a minimum of dermal absorption of DDT at unprotected skin areas. Ac-

ording to lethal dose for 50% survival of the group values reported by Gaines,¹² technical DDT is less toxic dermally to white rats than was a large percentage of the many pesticide compounds he tested. Draize et al,¹⁵ following a study of percutaneous absorption of DDT, concluded that DDT in the dry or powdered form is poorly absorbed by the skin. Although the health status of workers in this study was not specifically examined, the fact that they did not report any illness related to their DDT exposure correlates well with low human toxicity of DDT from other studies.^{1,2,6}

Even though the absorption of DDT through the skin is not as great as with certain other pesticides, such as organophosphorus compounds, it seems advisable to use

protective clothing to cover as much of the skin area as possible in order to avoid absorption and storage of the compound in the body. Where exposure is to dry formulations of the compound, the respiratory route takes on increased significance and warrants the use of tight-fitting filter cartridge-type respirators when working in areas of greater contamination within the formulating plant. When a great reduction of potential exposure can be brought about with the use of special protective gear, as shown in this study, it seems negligent for any employer to allow less protection even if a compound has a low toxicity.

Dorothy Fillman assisted with the insecticide determinations.

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An Additional Note regarding Measurement of the Exposure of Workers to Pesticides

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Since the submission for publication of our recent paper regarding methods for measuring the exposure of workers to pesticides,^a the authors have learned from Dr Henry F. Smyth, Jr, of the Mellon Institute (personal communication) of an additional technique that appears to be useful for determining the dermal absorption of pesticides by exposed individuals.

The procedure involves estimation of total absorption of a chemical from measurement of the chemical or its biotransformation product (or products) in the urine. Respiratory absorption is assumed to be equivalent to respiratory exposure, and is estimated on the basis of the concentration in air of the chemical under study and of an assumed tidal volume and respiratory rate for the exposed individual or by other applicable procedure. Dermal absorption is calculated by the difference between total absorption and respiratory absorption. This method is biased in favour of respiratory exposure. Not only the portion of the dose carried to the depth of the lungs but also the portion that is inhaled, deposited in the upper respiratory tract, carried into the pharynx, and eventually swallowed is counted as respiratory exposure. However, depending on particle size, much of the chemical in air may never be inhaled. Furthermore, part of the material inhaled may later be exhaled and not retained. Finally, the efficiency of recovering the compound or its derivative from urine may be imperfect. All of these factors would tend to overemphasize the importance of respiratory exposure and therefore underestimate the importance of dermal exposure. However, if one can exclude the possibility of direct oral ingestion, the result obtained through use of the method should represent a minimal value for dermal absorption.

The method may be considered as the most general application of the principle in which dermal absorption is made equivalent to total absorption (and to

total excretion) by preventing respiratory exposure through use of a pure air supply. The measurement of urinary excretion of the pesticide or its metabolite then provides an estimate of dermal absorption. This latter technique was used by Dutkiewicz^b for aniline and proposed independently by the group at the Phoenix, Ariz., Toxicology Laboratory of the Communicable Disease Center, Public Health Service, to estimate dermal absorption of parathion (unpublished results). Another variation of the technique makes it possible to estimate respiratory absorption by covering the entire skin area with completely impervious clothing to rule out dermal absorption, thereby making total exposure (or excretion) equivalent to respiratory absorption.

In preliminary work carried out at our laboratory, the Smyth technique has been used to calculate the absorption of parathion by spraymen during actual spray operations in orchards. The data used in these calculations were collected during the 1959 season in the course of a survey designed to study the relationship between parathion exposure and excretion of *p*-nitrophenol. There were ten spraymen in the experiment. One man was studied on two different occasions. For each sprayman, the total parathion absorbed was based on total urinary excretion of *p*-nitrophenol for several days (until a non-significant excretory level was reached) after the single spray exposure under study. Respiratory absorption was considered to be equivalent to respiratory exposure and was calculated for the time the worker actually sprayed on the day under study by using the mean parathion respiratory exposure (0.019 mg/hour) as determined for air-blast sprayers (Wolfe et al., unpublished observations), using the respirator-pad technique described in our recent paper.^a In one instance, the value (0.015 mg/hour) used was determined for the individual under study at a

^a Durham, W. F. & Wolfe, H. R. (1962) *Bull. Wld Hlth Org.*, 26, 75.

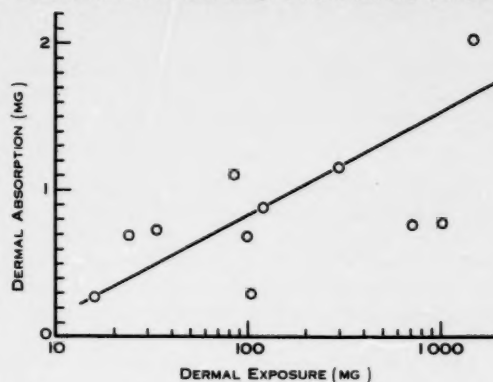
^b Dutkiewicz, T. (1961) In: *Proceedings of the 13th International Congress on Occupational Health, July 25-29, 1960*, New York, Book Craftsmen Assoc. Inc.

different time. The dermal exposure was estimated for each sprayman under his actual work conditions, using the alpha-cellulose pad technique.

The results are shown in the accompanying table. For each of the 11 spray exposures studied, a positive value was obtained for the calculated dermal absorption. The calculated dermal absorption, in each instance, was greater than the estimated respiratory absorption. The dermal absorption represented, as an average, 76.2% of the total absorption. However, the dermal absorption represented only a small percentage (range 0.1%-2.8%; mean 0.9%) of the dermal exposure. There was, in general, a rather good correlation between dermal exposure and dermal absorption. A plot of this relationship, as shown in the graph opposite, suggests that the correlation may be logarithmic rather than linear.

These results are presented as the best example of the Smyth technique available at this time. The use of average values may obscure details but should not lead to any important error. Ideally, estimation of respiratory exposure should be based on individual

RELATIONSHIP BETWEEN DERMAL EXPOSURE TO PARATHION SPRAY, AS MEASURED BY THE EXPOSURE-PAD TECHNIQUE, AND DERMAL ABSORPTION OF PARATHION, AS ESTIMATED BY THE SMYTH PROCEDURE, FOR ORCHARD SPRAYMEN



measurements, preferably by means of air samples taken in the breathing zone of the workers. (Respiratory-pad samples taken from the same worker

CALCULATED DERMAL ABSORPTION OF PARATHION BY SPRAYMEN DURING ORCHARD SPRAYING

Sprayman No.	Total urinary parathion excretion (mg)	Respiratory exposure			Dermal exposure			Calculated dermal absorption (excretion minus respiratory exposure)		
		mg/hour	Hours of exposure	Total mg	mg/hour	Hours of exposure	Total mg	Total mg	Proportion of total	
									Excretion (%)	Dermal exposure (%)
1	1.15	0.019 ^a	19.5	0.37	52.70	19.5	1027.65	0.78	68.0	0.08
2	0.34	0.019 ^a	2.75	0.05	37.90	2.75	104.23	0.29	84.7	0.28
3	0.83	0.019 ^a	4	0.08	8.60	4	34.40	0.75	90.8	2.18
4A	1.43	0.019 ^a	17.5	0.33	4.80	17.5	84.00	1.10	76.9	1.31
4B	1.06	0.019 ^a	16	0.30	44.15	16	706.40	0.76	71.6	0.11
5	0.47	0.019 ^a	10	0.19	1.61	10	16.10	0.28	59.5	1.73
6	1.42	0.015	17	0.25	17.4	17	296.50	1.17	82.4	0.39
7	1.17	0.019 ^a	15.95	0.30	7.50	15.95	119.63	0.87	74.2	0.73
8	0.91	0.019 ^a	11.75	0.22	8.20	11.75	96.35	0.69	75.5	0.71
9	0.85	0.019 ^a	9	0.17	2.70	9	24.30	0.69	80.1	2.82
10	2.35	0.019 ^a	15.5	0.29	93.90	15.5	1455.45	2.06	87.5	0.14
Mean	1.09	—	—	0.23	—	—	356.52	0.86	77.4 ^b	0.96 ^b

^a Mean respiratory exposure for air-blast sprayers.

^b Based on individual proportions.

would prevent his inhalation of insecticide so that his excretion would represent dermal absorption only.) In themselves, the results of this study have no clinical significance, because the highest rate of absorption involved (0.14 mg of *p*-nitrophenol per hour) would not be expected to produce any clinical effect or a marked inhibition of cholinesterase.^c To put it another way, the highest measured dose was 2.35 mg of parathion, distributed over a period of 15.5 hours, whereas Edson^d found that daily oral doses of 3 mg were tolerated by volunteers without cholinesterase depression or clinical effect.

^c Arterberry, J. D., Durham, W. F., Elliot, J. W. & Wolfe, H. R. (1962) *Arch. environ. Hlth*, 3, 476.

^d Edson, E. F. (1957) *The effects of prolonged administration of small daily doses of parathion in the rat, pig and man* (unpublished report from Fisons Pest Control Ltd.).

The results do offer additional evidence that men applying liquid sprays under the conditions in the Wenatchee, Wash., area are at risk of absorbing a relatively large amount of parathion through the skin. Therefore, in addition to taking precautions to avoid respiratory absorption of this pesticide, the sprayman should also give attention to covering his skin.

Conditions of exposure to pesticides vary greatly, and the relative importance of respiratory and dermal absorption may vary accordingly.^e It is hoped that the Smyth technique will be further used, for quantitative data obtained in this way would certainly be useful in defining the variation and thus permitting selection of appropriate protective measures.

^e Goldblatt, M. W. (1950) *Pharm. J.*, 164, 229.

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PUBLICATION

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SURVEY OF INSECTICIDE SPRAY PRACTICES USED IN THE FRUIT ORCHARDS OF NORTH CENTRAL WASHINGTON

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A SURVEY was made of the spray practices used to apply D, D, T, and parathion in the orchards of north central Washington. These data were needed as background material concerning the exposure of workers and concerning the amount of residue on fruits grown in orchards in which spray practices are carried out.

The survey was made during 1951 and 1952 and was based on data from 806 individual operations chosen at random from approximately 6,800 operations used to control insects on fruit trees in the Wenatchee and Okanogan Valleys. These valleys yield approximately half of the apples grown in the state of Washington. A large majority of the 806 operations on which the survey was based were carried out in accordance with recommendations published in 1951 and 1952¹ by the Agricultural Experiment Stations of the State College of Washington. In general, both D, D, T,² and parathion³ are applied in a single finished formulation. The rate of distribution per single application and the rate per season were studied.

The data have been tabulated with respect to the type and concentration of the formulation and the rate and method of application for the two major insecticides—D, D, T, and parathion. Table 1 gives the high, low, and mean of the rate per acre per application of insecticide⁴ when applied as a constantly agitated water suspension⁵ or as an emulsion to 237 orchards by stationary power-driven equipment,⁶ to 318 orchards by truck- or tractor-drawn, power-driven equipment, and to 61 orchards by airplanes. The concentration and the rate of application of the formulations are also included as auxiliary information.

Table 2 gives the high, low, and mean of the rate per acre per application of insecticide when applied as a dust to 172 orchards by aircraft, including airplanes and helicopters, and to 18 orchards by truck- or tractor-drawn, power-driven equipment.

From the Communicable Disease Center, Public Health Service, United States Department of Health, Education, and Welfare, Atlanta.

1. Spray Recommendations for Tree Fruits in Eastern Washington. Extension Bulletin 419, State College of Washington, Agricultural Experiment Stations, Pullman, Wash., March, 1952.

2. 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane.

3. O,O-diethyl O-*p*-nitrophenyl thiophosphate.

4. It is not practicable to give the rate per tree, since there is little consistency in the number of trees per acre.

5. The term water suspension is used to cover those liquid formulations prepared by suspending water-wettable powders in an aqueous medium.

6. Locally spoken of as hand-spray equipment.

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From a toxicological standpoint, the most important revelations in these tables are that D. D. T. was applied in the fruit orchards of north central Washington at rates of 1.0 to 25.0 lb. per acre per application and that parathion was applied at rates of 0.2 to 9.8 lb. per acre per application. The average rate per acre per application was 10.1 lb. for D. D. T. and 1.8 lb. for parathion. The rate of application per acre per season was approximately 20.3 lb. of D. D. T. and 3.7 lb. of parathion. Two applications are made on an average per season, and these usually occur in May and June. A slight variation occurred during 1952, since some growers used three applications of parathion due to the shortage of lime sulfur

TABLE 1.—Summary of the Rates and Concentrations of D. D. T. and Parathion Water Suspensions and Emulsions Applied to Fruit Orchards in North Central Washington*

Method of Application	Values	Spray Gal./Acre	D. D. T.			Parathion		
			Lb./100 Gal. Spray	Per Cent Formulation W/V	Lb./Acre Application	Lb./100 Gal. Spray	Per Cent Formulation W/V	Lb./Acre Application
Stationary power-driven equipment (237 applications)	Highest	3,200	1.5	0.18	22.5	2.0	0.24	5.0
	Lowest	100	< 0.1	< 0.01	1.0	0.01	0.001	0.2
	Mean	1,400	0.9	0.10	13.1	0.2	0.03	2.3
Portable power-driven equipment (318 applications)	Highest	1,800	50.0	6.00	25.0	6.0	0.72	9.8
	Lowest	33	0.5	0.05	1.5	0.1	0.01	0.2
	Mean	450	6.8	0.93	9.4	1.1	0.13	1.6
Aircraft (61 applications)	Highest	20	50.0	6.00	10.0	25.0	3.00	5.0
	Lowest	20	10.0	1.20	2.0	5.0	0.60	1.0
	Mean	20	30.9	3.71	7.0	12.0	1.44	2.5

* These values are based on the amount applied per acre per application. (The large majority of the orchards receive at least two insecticide applications during the growing season.)

TABLE 2.—Summary of the Rates and Concentrations of D. D. T. and Parathion Dust Applied to Fruit Orchards in North Central Washington*

Method of Application	Values	Dust Lb./Acre	D. D. T.		Parathion	
			Per Cent Formulation W/W	Lb./Acre Application	Per Cent Formulation W/W	Lb./Acre Application
Aircraft (172 applications)	Highest	50	25.00	12.5	4.00	2.0
	Lowest	50	30.00	10.0	2.00	1.0
	Mean	50	23.96	12.0	2.60	1.3
Portable power-driven equipment (18 applications)	Highest	60	30.00	12.0	2.68	1.6
	Lowest	60	17.86	10.7	2.00	1.2
	Mean	60	18.30	10.3	2.40	1.4

* These values are based on the amount applied per acre per application. (The large majority of the orchards receive at least two insecticide applications during the growing season.)

which is usually used as a dormant spray. When D. D. T. and parathion were applied in a single formulation, the ratio of D. D. T. to parathion was always greater than 1, being about 2 to 1 in favor of D. D. T. in the case of finished liquid formulations and about 10 to 1 in favor of D. D. T. in the case of dusts.

Considering all methods of application, the liquid formulations, including water suspensions and emulsions, were used about three times more frequently than were dust formulations. In the early part of the growing season the ratio was even higher in favor of the liquid formulations, while in the latter part of the season the ratio was approximately 1 to 1.

The finished liquid formulations were much less concentrated than were the corresponding dust formulations. However, the liquid formulations were applied at a

much higher rate per acre. Thus, the rate of application of insecticide was approximately the same from both types of formulations. In estimating operator exposure and possible residue, the difference in the concentrations of these two types of formulations should be taken into account, along with the physical difference between the liquid formulation and the dry solid dust.

It should be pointed out that 90% of the finished liquid formulations were applied by ground equipment and that about the same proportion of dust formulations were applied by aircraft.

While this report is confined to the major insecticides used in the area—D. D. T. and parathion, consideration should be given to the fact that other insecticides, mainly tetraethyl pyrophosphate, Aramite,⁷ malathion,⁸ and methyl parathion,⁹ as well as fungicides, for example, sulfur compounds, and plant growth regulators, for example, α -naphthaleneacetic acid and 2,4-dichlorophenoxyacetic acid (2,4-D), are being applied to the orchards of north central Washington.

In a separate study now under way, a number of air samples have been collected in areas receiving applications of D. D. T. and parathion. The latter studies, especially as they related to hazards to human beings, will be reported in a separate publication.

7. Manufactured by Chemical Division of the United States Rubber Co., Naugatuck, Conn.

8. S-(1,2-dicarbethoxyethyl)O,O-dimethyl dithiophosphate.

9. O,O-dimethyl O-*p*-nitrophenyl thiophosphate.

PESTICIDES IN PEOPLE

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CRITERIA FOR MONITORING PESTICIDES IN PEOPLE INCLUDE HIGH- AND LOW-EXPOSURE CONDITIONS, AGE, SEX DIFFERENCES

Anne R. Yobs¹

As described here the program for assessing pesticide residue levels in the Nation's populace is being carried out by the Pesticides Program, National Communicable Disease Center, Bureau of Disease Prevention and Environmental Control, Public Health Service, U. S. Department of Health, Education, and Welfare.

Monitoring Objective

The purpose of the human monitoring program is to determine on a national scale the levels and trends of certain more commonly used pesticide chemicals, both in the general population and in population segments where the occurrence of more extensive exposure to pesticides is known or suspected.

In the past, studies were made by various investigators assessing the concentration of pesticides and/or their metabolites in human beings. These studies have provided a useful body of information concerning the relationship of exposure to the human body's storage of pesticides. However, such assessments were limited in regard to the geographic coverage of the sampling, the variety of conditions of exposure, and the spectrum of pesticides investigated. They were also limited in the age range, the sex distribution, and the size of the sampled population. Probably the greatest weakness in the earlier studies was the limited variety of body tissues tested. In fact, this earlier work was essentially limited to body fat. The present monitoring program will provide statistically and epidemiologically sound information for use in the evaluation of the significance of man's total exposure to pesticides.

¹ Pesticides Program, National Communicable Disease Center, Public Health Service, Bureau of Disease Prevention and Environmental Control, U. S. Department of Health, Education, and Welfare, Atlanta, Georgia 30333.

Program Design, Samples, and Sampling Sites

Monitoring studies will be of two types, a limited national survey of the general population and an in-depth study of selected communities in high-use areas.

In the survey being activated in calendar year 1967, tissues will be collected regularly from the general population in 12 different areas of the country. The number of specimens will be relatively small at first to permit evaluation of the approach and correction of any problem areas. The program will be expanded later as data indicate. Samples will be collected at post-mortem examinations and from hospitalized patients. Only body fat samples will be analyzed at this time from post-mortem examinations. Sample tissues from living patients will include blood serum and adipose tissue removed incidentally at surgery.

In-depth community studies, including monitoring, are in progress at these locations:

Arizona — Pima and Maricopa Counties
California — State-wide
Colorado — Weld County
Florida — Dade County
Hawaii — Island of Oahu
Iowa — Johnson County
Louisiana — LaForte and Jefferson Parishes
Michigan — Berrien County
New Jersey — Monmouth County
Texas — Cameron and Hidalgo Counties
Washington — Wenatchee and Quincy Basins

Plans are under way for the initiation of additional studies in Idaho, South Carolina, Mississippi, and Utah.

These studies are sampling three population groups: (1) occupationally exposed workers, (2) individuals not occupationally exposed but known to be repeatedly exposed, and (3) the general urban population. The occupationally exposed group consists of one or more of the following: agricultural applicators, workers in pesticide formulating plants, pest control operators, greenhouse workers, and aerial spray pilots. Representatives in the repeatedly exposed population are people living in environments where they may be expected to have repeated nonoccupational exposure—these areas are usually heavily agricultural. The general urban population group represents individuals whose exposures are largely limited to pesticide traces in food, water, and air plus occasional

household or garden use of pesticides. Since the occupationally exposed group consists predominantly of men, sampling of this group will be restricted to adult males. However, the two remaining groups will be equally divided between males and females with a reasonable age spread.

Study procedures for each participant include a detailed history of pesticide exposure and usage, a complete medical history and physical examination, and hematologic and biochemical testing. Pesticide residue analyses will be performed on urine and blood of all participants and, when available, on body fat and other tissues also. In addition, each study performs an area pesticide-usage profile and analyzes samples from the local environment. Tissues taken by the Community Studies for general population studies will be secured at post-mortem examinations of accidental deaths.

Pesticides and Analytical Methods

Chlorinated hydrocarbon pesticides are known to concentrate in animal and human fat and to persist there for prolonged periods. Primary emphasis will be given to detecting residues from these chemical compounds and assessing their levels. A serious problem is the lack of suitable analytical procedures for detecting different classes of pesticide chemicals in the ranges expected in the general population and applicable to several tissues. It is recognized that human tissue samples may well contain several pesticides of the same or other classes, and the analysts will be expected to be alert to identify them. As research progress may indicate and require, and as technological developments permit, other tissues and other pesticides may be added to this monitoring program.

Each Community Study has or is developing laboratory competence in pesticide analysis and the required hematological and biochemical testing. They perform all testing for their own locations, and some will perform the analytical testing for the general monitoring program using standardized procedures. All participating laboratories are required to maintain a satisfactory standard of technical performance as demonstrated in a quality control program conducted by the Pesticide Research Laboratory (Florida) of the Pesticides Program.

Standardization of Procedures

Guidelines and forms have been developed to standardize the collection and recording of information, the sampling and handling of tissue specimens, and laboratory test procedures. This will permit the comparison of data among the several participants in the monitoring program. Information from the several study areas will be combined to give an overall picture for the Nation as a whole.

PESTICIDES IN PEOPLE

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Total Mercury Levels in Selected Human Tissues, Idaho—1973-74^{1,2}

J. Gabica, W. Benson, and M. Loomis

ABSTRACT

Total mercury levels were determined in human tissues taken at autopsy from six hospitals in the three basic geographical areas of Idaho. Of the 242 specimens analyzed, 76 percent contained detectable mercury. Levels were compared with respect to the age, sex, and geographic residence of autopsied individuals. Mean levels detected were 1.04 ppm in kidney tissue, 0.34 ppm in liver, and 0.08 ppm in brain. Mean mercury levels for the three geographical areas were: southeastern Idaho, 0.22 ppm; southwestern Idaho, 0.80 ppm; and northern Idaho, 0.43 ppm. The relatively high means in southwestern Idaho specimens may be related to the preponderance of natural cinnabar deposits in that portion of the State. Mercury levels were higher in women than men for all tissues in both the southwestern and northern areas, but the reverse was true in the southeast. Data were compared with findings of other investigators in an attempt to arrive at background levels of total mercury residues in human tissues.

Introduction

Data on mercury levels in human tissues are limited. Mercury has not been included in most comprehensive studies on trace metals in human tissues. Analytical difficulties may offer a partial explanation for this exclusion (1, 2).

Knowledge of background levels of mercury in various human tissues is important because of the possible mutagenic effects or toxic properties of this element and its various compounds. Any use of mercurials as diuretics, antiseptics, cathartics, or pesticides (3-6) would presumably contribute to mercury found in various body tissues. Naturally occurring cinnabar ore deposits may be an additional source of exposure in Idaho with its extensive history of mining in which large quantities of

metallic mercury were used to extract gold from ore (7). Some of this mercury is still present in large quantities in certain locations, especially streambeds throughout the State (8).

The present study was intended to be a preliminary screening of a survey of mercury levels in certain tissues of humans and a wide variety of wildlife. Cause of death was noted in each instance but was not compared to mercury concentrations found.

Autopsy and Sampling Procedures

The State was roughly divided into three general areas, northern Idaho, southwestern Idaho, and southeastern Idaho, relating to the locations of the six participating hospitals (Fig. 1). The hospitals, two of which were

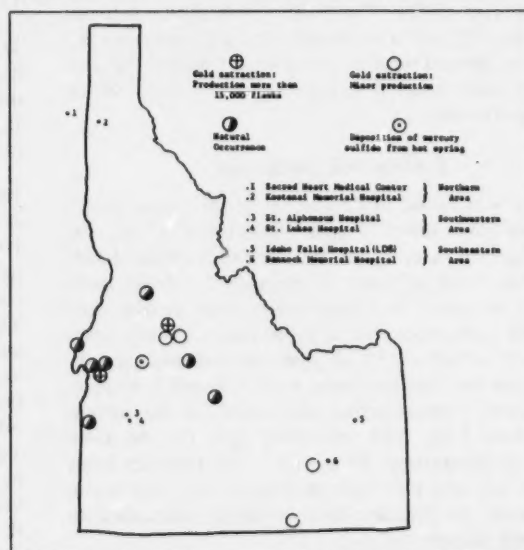


FIGURE 1. Map of Idaho showing sites of sampling, natural mercury deposits, and gold mining

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² Epidemiologic Studies Program, Department of Health and Welfare, Statehouse, Boise, Idaho 83720.

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located in each of these three areas, contributed 242 autopsy samples of kidney, liver, and brain tissues from patients who had died during the previous 12 months from a variety of causes unrelated to mercury poisoning. Because tissues analyzed were from autopsies, they could not be considered normal. However, mean levels drawn from individual cases should be close to normal.

Specimens were placed immediately in formaldehyde at the respective hospitals and sent to the laboratory at once or, in some cases, no more than 2 weeks before analysis. Formalin was analyzed before use and again after autopsy specimens had been stored in the solution. In no instance was mercury or any other background contaminant detected which might invalidate values obtained. Researchers selected homogeneous samples from each organ for analysis, taking care to prevent pre-analytical contamination from handling. All glassware used was scrupulously cleaned with nitric acid and rinsed with distilled water.

Tissue specimens were placed on blotting paper and allowed to dry until most of the formalin had been absorbed or evaporated. Subsequently, a 1-5-g sample was ground in a Dual glass tissue grinder; a 1-g wet-weight sample was then removed for analysis. Results are based upon this 1-g sample. The sample was digested according to procedures outlined by the American Association of Analytical Chemists (9). Fifty ml distilled water was added to a 50-ml aliquot of the digest and placed in a 200-ml biological oxygen demand (BOD) bottle. Two ml of a 5 percent potassium persulfate solution, 4 ml of a 5 percent KMnO_4 solution, 2 ml of a 100-ml water solution containing 12 g NaCl and 12 g hydroxylamine, and 5 ml of a 10 percent SnCl_2 solution were added. The mixture was stirred between additions (8) and was immediately put under an air vaporizer. Results were recorded on a Coleman 50 analyzer by cold vapor. A standard curve of 0.01-2.00 μg mercury was used.

Results and Discussion

Mercury was found in 76 percent of all tissues tested; the mean value was 0.73 ppm. Mean levels by age, sex, and geographic area of the State for each of the tissues tested are listed in Table 1. Roughly 3.5 times more mercury occurred in kidney tissue than in liver and about 10 times more than in brain tissue. Kidney levels ranged to a high of 15.70 ppm, whereas highest concentrations for liver and brain were 5.80 and 0.94 ppm, respectively. Corresponding mean levels in the current study were 1.04, 0.34, and 0.08 ppm for the same tissues. In comparison, Matsumoto (10) reported levels of 6.60, 4.0, and 0.50 ppm in kidney, liver, and brain, respectively, in Japanese fetuses which succumbed to Minamata disease (10, 11).

Hospitals with the highest mercury levels in all three organs were located in southwestern Idaho where most

of the natural mercury deposits are found (see Fig. 1 in reference 7). The combined mean level for all tissues was 0.80 ppm in the southwest, whereas the mean level was only 0.22 ppm in the southeast and 0.43 ppm in the north. Nevertheless, it cannot be assumed that these deposits caused the higher levels. High concentrations were not found in this geographical area during a previous study by Benson and Gabica in which 1,000 hair samples from residents throughout the State were analyzed for total mercury (12).

Table 2 and the Benson/Gabica study (12) show that mercury levels vary according to sex of the subject once they approach or exceed 1 ppm. In general, levels in women were higher than those in men. Women over 65 years of age had more mercury in their tissues than had men in the same age group. The converse was true for people in the 46-55- and 20-45-year age groups although it was less marked in the latter. The higher mercury levels in females of advanced age have not been explained. No available data show evidence of differences in the environmental exposure of males and females. Differences between residue levels in the different sexes cannot be attributed to cosmetics used on skin and hair because the same distribution with respect to sex was found in all organs.

Mean residue concentrations in liver were higher in women than in men from all areas. Women also had higher average levels in the brain and kidney except for kidney tissue in the southeast and brain tissue in the north. Total residues for all three areas were higher among women in all tissues except kidney; in those tissues total values for men were slightly higher (Table 1).

Dal Cortivo et al. (13) found that brain, liver, and kidney tissue from autopsy specimens had respective mean mercury levels of 0.05, 0.10, and 0.20 ppm. On the other hand, Kevorkian et al. (2) found much higher mean levels: 0.25, 7.70, and 10.36 ppm, respectively.

Hyland et al. (1) and Howie et al. (5) reported results similar to those of the present study except that Hyland found only 0.65 ppm mercury in kidney samples. Howie's results were corrected from dry to wet weight for comparison by dividing values by five. Takeuchi (14) showed that mercury levels in cats averaged 2.00 ppm in the liver, 0.41 ppm in the kidney, and less than 0.10 ppm in the brain. This differs from the findings of the present study and from those of others in which highest concentrations were in kidneys. Takeuchi, however, is in accord with the present study in finding lower mercury levels in human brain tissue than in liver and kidney tissue. This is probably due to the selectivity of the blood/brain barrier, especially with respect to inorganic mercury (15). This barrier would not be active in the deposition of mercury into tissue of such organs as liver or kidney.

TABLE 1. Distribution of mercury concentrations in tissue from human autopsy samples, Idaho—1973-74

AREA	TISSUE	SEX	NO. SAMPLES	POSITIVE SAMPLES, %	MEAN, PPM	RANGE, PPM
Southeast	K	M	14	93	1.07	0-3.04
		F	3	67	0.06	0-0.20
		M and F	17	88	0.56	0-3.04
	B	M	13	92	0.02	0-0.06
		F	1	100	0.02	0-0.02
		M and F	14	96	0.02	0-0.06
	L	M	18	78	0.06	0-0.41
		F	8	38	0.15	0-0.25
		M and F	26	58	0.11	0-0.41
	Total	M	45	88	0.39	0-3.04
		F	12	62	0.05	0-0.25
		M and F	57	78	0.22	0-3.04
Southwest	K	M	24	71	1.27	0.02-15.70
		F	22	96	1.90	0.18-12.50
		M and F	46	83	1.57	0.02-15.70
	B	M	9	89	0.11	0-0.16
		F	11	91	0.28	0-0.95
		M and F	20	90	0.19	0-0.95
	L	M	25	100	0.34	0.1-2.11
		F	24	100	0.95	0-5.07
		M and F	49	100	0.64	0-5.07
	Total	M	58	87	0.57	0-15.70
		F	57	96	1.04	0-12.50
		M and F	115	91	0.80	0-15.70
North	K	M	20	75	0.84	0-7.56
		F	11	91	1.14	0-5.78
		M and F	31	83	0.99	0-7.56
	B	M	6	83	0.04	0-0.25
		F	2	50	0.01	0-0.01
		M and F	8	66	0.03	0-0.25
	L	M	18	28	0.06	0-0.49
		F	13	23	0.48	0-5.80
		M and F	31	26	0.27	0-5.80
	Total	M	44	62	0.31	0-7.56
		F	26	55	0.54	0-5.80
		M and F	70	58	0.43	0-7.56
Statewide	K	M	58	80	1.06	0-15.70
		F	36	92	1.03	0-12.50
		M and F	94	86	1.04	0-15.70
	B	M	28	88	0.06	0-0.25
		F	14	80	0.10	0-0.94
		M and F	42	84	0.08	0-0.94
	L	M	61	69	0.15	0-2.11
		F	45	54	0.53	0-5.80
		M and F	106	61	0.34	0-5.80
	Total	M	147	79	0.64	0-15.70
		F	95	73	0.82	0-12.50
		M and F	242	76	0.73	0-15.70

NOTE: K = kidney
L = liver
B = brain
M = male
F = female

TABLE 2. Mercury levels in tissue from human autopsy samples, Idaho—1973-74

AGE RANGE, YEARS	TISSUE	SEX	NO. SAMPLES	RANGE, PPM	MEAN, PPM
0 - 19	B	M	7	0.00-0.73	0.07
		F	5	0.00-0.35	0.14
	L	M	8	0.00-1.11	0.12
		F	7	0.00-5.07	0.95
	K	M	4	0.01-0.64	0.11
		F	5	0.00-1.16	0.37
20 - 45	B	M	3	0.00-0.08	0.05
		F	4	0.06-0.16	0.05
	L	M	8	0.00-0.37	0.19
		F	5	0.00-0.41	0.14
	K	M	8	0.00-3.04	0.77
		F	4	0.05-0.85	0.33
46 - 55	B	M	2	0.00-0.05	0.02
		F	1	0.00-0.04	0.06
	L	M	8	0.00-2.40	0.33
		F	9	0.00-1.06	0.25
	K	M	11	0.01-7.56	2.95
		F	7	0.00-4.40	0.95
56 - 65	B	M	7	0.00-0.16	0.02
		F	2	0.00-0.14	0.08
	L	M	12	0.00-0.31	0.06
		F	8	0.00-2.26	0.63
	K	M	12	0.00-7.56	0.58
		F	7	0.00-0.91	0.50
66 - 75	B	M	6	0.00-0.01	0.00
		F	2	0.00-0.26	0.56
	L	M	16	0.02-0.09	0.11
		F	9	0.00-0.31	0.75
	K	M	15	0.00-0.66	0.26
		F	7	0.04-9.40	5.37
76 - 86	B	M	1	0.00-0.02	0.02
		F	1	0.00-0.33	0.33
	L	M	8	0.00-0.90	0.11
		F	8	0.00-5.80	1.00
	K	M	8	0.02-1.55	0.48
		F	6	0.00-12.50	0.74

NOTE: B = brain
 L = liver
 K = kidney
 M = male
 F = female

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PROTECTION OF SHADE TREES WITH DDT AND ITS RELATION TO HUMAN HEALTH

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PUBLICATION

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ABSTRACT

The toxicological properties of DDT have been studied thoroughly. Volunteers have ingested 35 mg. of DDT per day for 18 months, and occupational exposure of this magnitude can occur for as long as 6½ years with no apparent ill effects. Since the exposure of the spray operators and particularly the general public to this insecticide will be much less than the above amounts, it is anticipated that there will be no difficulties due to exposure to DDT during the program to control Dutch elm disease.

We have been asked, as a representative of the Toxicology Section of the Communicable Disease Center, to discuss the effects of the program to control Dutch elm disease on the health of the men who spray the DDT and on the health of the people who live near the trees that are sprayed.

DDT, the insecticide used in this program, was the first of the new synthetic organic insecticides to be employed on a world-wide scale. This compound has been of great use not only in agriculture but also in the control of insect-borne diseases. It has been estimated that over 39 diseases, some of which are the most important in the world, can be partially or completely controlled with DDT. It has been possible to stop epidemics of such diseases as malaria, plague, and louse-borne typhus.⁽¹⁾ Although some species of insects have developed resistance to DDT, and although a great many other synthetic insecticides have been prepared, DDT is still the most important from a quantitative standpoint, since approximately one out of every four pounds of synthetic organic insecticide produced in 1958 in the United States was DDT. Another indication of the

widespread use of this insecticide is shown in the large increase in annual U. S. production, which has risen from 50,000,000 lb. in 1947 to 140,000,000 lb. in 1958, the last year for which we have complete figures.⁽²⁾ The widespread use of DDT in agriculture is reflected by the presence of DDT in food, particularly in the fat portion of meat,⁽³⁾ and also by the presence of the compound in the fat of people in the general population.⁽⁴⁻⁶⁾

Much research has been done on the toxicology of DDT. The results of these experiments, as well as the extensive experience in its use, have given a great deal of information about the toxicology and pharmacology of this compound, although the basic mode of action of this insecticide is still unknown.

Since its beginning in 1949, the CDC Toxicology Program has had a two-fold objective: First — to learn the toxicity and mode of action of the pesticides, including the insecticides; second — to bring this information to those who need it in order that these valuable materials may be used safely. In view of the widespread use of DDT, one of the major projects of our group has been concerned with the toxicity of this insecticide to

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man. Our experiments have included the experimental exposure of man or animals to DDT, studies of cases of accidental poisoning, and field studies of the health of men who work with this compound. The storage of DDT in the bodies of the general population has been investigated, and the DDT content of typical meals has been determined.⁽³⁾

For these studies, it has been necessary to devise practical methods of measuring the actual amount of DDT absorbed, since in any epidemiologic study of illness supposedly associated with a chemical, it is desirable to show with some objective test that the subject actually has absorbed some of the compound under question. The following studies of the fate of DDT administered to animals and men have provided us with such tests.

When DDT (2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane) is fed to animals or to man, some of the compound is converted to DDE (2,2-bis(p-chlorophenyl)-1,1-dichloroethylene)^(5,6) and DDA (bis-(p-chlorophenyl) acetic acid) and other⁽⁷⁻¹⁰⁾ compounds of unknown structure.⁽⁷⁻¹²⁾ Some of the DDT or DDE is stored in the fat depots, the rest is excreted in the bile, whereas the DDA is excreted in the bile and urine.

Those who manufacture, formulate, or apply DDT are more likely to absorb a small daily amount of the insecticide rather than a single large dose. Therefore, one of the major research projects of the Toxicology Section has been to study the effects of small daily doses of DDT in animals or man. It has been found that, if an animal or man is given a small dose of this compound each day, the content of both DDT and DDE in the fat depots gradually builds up and the amount of DDA excreted in the urine increases. Eventually a point is reached at which the amount of DDT taken in is balanced by the amount excreted. This condition is called storage equilibrium. Under these circumstances, the concentration of DDT present in the fat and the amount of DDA excreted in the urine are proportional to the amount of DDT ingested.⁽¹⁰⁾ Thus, we have two methods of measuring the amount of DDT absorbed by a given individual. First, a fat sample can be removed by biopsy from the subject and analyzed for its content of DDT and DDE. Second, the DDA content of a urine sample can be measured. Then the amount of DDT absorbed can be stated in relation to the DDT content of the fat or the DDA content of the urine of men who have ingested known amounts of DDT. Many of the older studies were based on the assay of the DDT content of subcutaneous fat, but with the development of a sensitive chemical assay for DDA,⁽¹²⁾ the more convenient measurement of the DDA content of

the urine has been employed.

Having considered the fate of DDT in the body and the means of measuring the amount of DDT taken in, let us now discuss the toxic effects of a large dose of the compound. The main action of a poisonous dose of DDT is on the nervous system. An animal given a toxic dose of this insecticide will exhibit muscular tremor and incoordination, and in severe poisoning will have convulsions which may terminate in death. In man, an oral dose of about 0.7 gm. will produce sensation of burning or itching of the tongue, lips, and part of the face. These areas may be extremely sensitive to touch and to pain. The fingers and toes may lose vibratory sensation, and the subject may have poor coordination. At a higher level (about 1 gm.), the individual may also have muscular tremor and convulsions. Large doses induce vomiting so that the actual amount retained is difficult to estimate. However, men have recovered from swallowing as much as 20 gm. of DDT. All fatal cases of poisoning with DDT, with one possible exception⁽¹³⁾ have involved the ingestion of amounts of solvents which in themselves might be fatal, so that it is difficult to determine whether death was caused by the insecticide or by the solvent.⁽¹⁴⁾ A number of very serious illnesses have been caused by the accidental ingestion of DDT, however.⁽¹⁴⁾

The toxic properties of DDT are influenced markedly by the route of administration. Thus, DDT is less toxic when put on the skin than when given orally. This is due to a difference in the rate of absorption. In addition, the toxicity of DDT is influenced by the solvent in which it is dissolved. Solvents, such as fats and oils, increase the toxicity of DDT. The most pronounced effect of solvents is seen when DDT is applied to the skin, for this insecticide is much less toxic when applied as dry powder than when applied as a solution. There is practically no absorption of undissolved DDT by the skin. In fact, it is virtually impossible to put enough DDT in dry powdered form on the skin of an animal to kill him. Further evidence of the low dermal toxicity of DDT is that all fatal cases of DDT poisoning have involved ingestion of the compound rather than exposure to the skin alone.⁽¹⁴⁾

The low toxicity of DDT applied to the skin is of great practical importance in the safe use of this insecticide. Field studies of actual spray operations have shown that most of the exposure is dermal, rather than respiratory. This point is illustrated in a recent study of indoor and outdoor spraying which was conducted at our Wenatchee, Washington Field Station.⁽¹⁵⁾

In this experiment, five per cent DDT suspension was sprayed on a flat surface with a hand

operated sprayer. The wand was held approximately 15 to 18 inches from the surface, and the spraying was timed with a stopwatch. In all spraying operations, the applicator stood as far as possible out of the spray drift. Small pads containing filter paper were placed on various areas of the clothing of the man who was carrying out the spray operations. The subject also wore a respirator which contained a filter paper pad. After a measured interval of spraying, the pads were removed and the amount of DDT present was determined. The area of the filter paper pads and the area of various parts of the body were known. From these data, it was possible to calculate the dermal and respiratory exposure of the operator. Assuming he sprayed four hours out of an eight-hour day and that the head, neck, lower arms, and hands were bare, it was found that outdoor spraying gave a total dermal exposure of 972 mg. per day, whereas the respiratory exposure was 0.44 mg. per day; that is, there was about 2,000 times more exposure on the skin via the respiratory tract. The operator received even greater exposure when spraying was done indoors; 7020 mg. per day was deposited on the skin, and 28 mg. was caught in the respirator pads (a ratio of about 250 to 1). Ordinary clothing gives adequate protection against dermal exposure to DDT. In experiments similar to those previously described, when the absorbent pads were placed underneath a cotton shirt, less than five percent of the DDT penetrated the cloth.⁽¹⁴⁾

Let us now turn to the question of the effect of the program to control Dutch elm disease on the health of the spray operators. We have made no studies of the effects of DDT on men under the particular conditions of spraying used in the above program. However, in the experiments carried out on human volunteers by the Toxicology Section, men ingested 35 mg. of DDT per day for 18 months with no effects as noted by themselves or by careful medical examination except, of course, that the men excreted amounts of DDA in the urine and stored increased amounts of DDT and DDE in the fat. Under these conditions, after dosing for 10 months with technical DDT, the concentration of this substance in the fat ranged from 101 to 367 ppm and averaged 284 ppm⁽¹⁰⁾ as compared with the average for the general population of less than 10 ppm.⁽¹⁶⁾ In another survey conducted by our group, men who had received very heavy occupational exposure for as long as six and a half years in plants in which DDT is formulated were found to have no more illness or symptoms than a comparable group of the general population. These men worked without protective clothing, and in many cases, were covered with a thick coat of

concentrated DDT dust during the working day. Based on the DDA content of their urine, these men absorbed as much DDT per day as the volunteers who ingested 35 mg. per day for 18 months. These studies indicate that men can ingest 35 mg. of DDT per day for as long as six and a half years without any subsequent changes in their health as revealed by thorough physical examination, symptoms, or work-attendance records.⁽¹⁷⁾

The men who will carry out the spray program to control Dutch elm disease should receive far less exposure than the workers in formulating plants or the volunteers who ingested known amounts of DDT in their food. In a survey carried out by the Toxicology Section in the fruit growing area of Washington, it was found that the DDT content of the subcutaneous fat of agricultural spray operators was 17 ppm or only about three times the average for the general population.⁽¹⁸⁾ This result means that these agricultural workers have ingested the equivalent of 0.56 mg. of DDT per day or about 1.5 per cent of the amount safely ingested each day by the volunteers for 18 months and by formulating plant workers for as long as six and a half years.

The exposure to DDT of the spray operators in the Dutch elm disease program may be no more than that of these agricultural spray operators. It is true that the latter workers spray with less concentrated suspensions of DDT than do the former workmen, that is with as high as six per cent instead of 12 per cent DDT suspensions.⁽¹⁸⁾ On the other hand, since they spray low fruit trees rather than tall elm trees, the agricultural spray operators probably do closer direct overhead spraying and thus may encounter more splash-back of insecticide than do the spray operators in the Dutch elm disease program.

On the basis of the above studies and the long history of safe occupational use of DDT, we anticipate that there will be no difficulties with the health of the spray operators in the Dutch elm disease program related to the use of this insecticide if good spray practices are used. If the members of the Commission would like to find out how much DDT these men absorb in the course of their work, the Toxicology Section would be glad to analyze appropriate urine samples for DDA, if the samples are sent to us.

Finally, we should consider the possible effect of the control program on the health of the general population or to the people living near the trees to be sprayed. People who live in agricultural areas where extensive spraying with DDT is done several times a year over many acres of fruit trees have only a small increase of 1.1 ppm in the average

level of stored DDT, as compared to the average concentration of 4.9 ppm for the general population.⁽¹⁸⁾ Thus, they absorb only slightly more than the average member of the general population and 0.7 per cent of the amount of DDT ingested by workers in formulating plants for about six years with no apparent ill effects. The people who live near the trees to be sprayed undoubtedly will not be exposed to DDT as often as the individuals studied in the fruit growing areas. Thus, on the basis of our present knowledge of DDT, we do not believe that the health of the general public or the people living nearby the trees which are to be sprayed will be endangered.

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A Health Survey of Workers in a 2,4-D and 2,4,5-T Plant

With Special Attention to Chloracne,

Porphyria Cutanea Tarda, and

Psychologic Parameters

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A study of 73 male employees in a 2,4,5-T factory was made. Chloracne was found in 13 (18%) workers. Severity of chloracne correlated significantly with the presence of hyperpigmentation, hirsutism, eye irritation, and a high score on the manic scale of the Minnesota Multiphasic Personality Inventory. Chloracne was not, however, correlated significantly with job location within the plant, duration of employment, or coproporphyrin excretion. Although 11 subjects with uroporphy-

rinuria and at least three with overt porphyria cutanea tarda had been found in a study of the same plant six years ago, no clinical porphyria could be currently documented and only one worker had persistent uroporphyrinuria. Evidence of toxicity in other organ systems was markedly less than that reported in previous studies and could not be shown to differ from normal populations in most instances.

THE herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) are widely used throughout the world. Several distinct medical problems have been described in workers involved in the production of these compounds. These problems can arbitrarily be subdivided into (1) chloracne and mucous membrane irritation, (2) hepatotoxicity,

neuromuscular symptoms, psychologic alterations, and other systemic symptoms, and (3) porphyria cutanea tarda (PCT).

Chloracne and Mucous Membrane Irritation.—Chloracne (perna disease, perchloronaphthalene disease) has been described as an extremely refractory acne seen in workers involved in the production of several chlorinated aromatic compounds.¹⁻³ Kimmig and Schulz⁴⁻⁶ described this dermatologic condition in workers in a 2,4,5-T factory. The condition is characterized by inclusion cysts, comedones, and pustules, with eventual scarring, and originates in the temple-zygomatic area with spread to the pinna, nape of the neck, back, upper chest, and inguinal area. Many of these patients also had blepharoconjunctivitis. The investigators showed that purified 2,4,5-trichlorophenol (TCP) was not acnegenic, but that 2,3,6,7-tetrachlorodibenzodioxin (TCDD) isolated from the crude TCP reaction mixture was an extremely potent acnegenic agent when applied to rabbits' ears.⁴ The TCDD is con-

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sidered an important, but not necessarily the only, acnegenic compound in 2,4,5-T production.

Hepatotoxicity, Neuromuscular Problems, Psychologic Alterations, and Other Systemic Symptoms.—In addition to chloracne, studies of workers in 2,4,5-T plants have frequently noted other signs and symptoms suggestive of systemic toxicity. These include anorexia and weight loss, abdominal pains and postprandial flatulence, headaches, weakness in the legs, and hepatic dysfunction.⁶⁻¹⁰ The following psychological alterations were also noted: lack of vigor, drive, and libido; easy fatigability; emotional instability; and diminished ability to learn.

Porphyria Cutanea Tarda.—Porphyria cutanea tarda is an acquired porphyria, generally occurring in men after age 40, in which significant liver dysfunction and usually a history of alcoholic abuse are found. The syndrome consists of vesiculobullous lesions on areas of the body exposed to light, hirsutism, excessive mechanical fragility of the skin, hyperpigmentation, and excretion of red urine containing an increased amount of uroporphyrin or coproporphyrin, or both, but not a large increase in urinary δ -amino-levulinic acid (ALA) or porphobilinogen (PBG).^{11,12} Frequently these patients have hyperferremia and hemosiderosis, and phlebotomy often reverses the clinical picture and decreases porphyrin excretion.^{13,14}

In 1964, Bleiberg et al¹⁵ reported studies of 29 workers in a 2,4-D and 2,4,5-T factory. Many of the workers had chloracne and 11 had abnormal excretion of urinary uroporphyrins. Many of the workers with and without uroporphyrinuria had hirsutism, hyperpigmentation, and increased skin fragility. Liver dysfunction was noted in two hospitalized patients.

As a follow-up of the observations of Bleiberg et al¹⁵ of a toxic PCT in these factory workers, we restudied all the employees in the same plant in February 1969 with particular emphasis on PCT, chloracne, hepatotoxicity, and neuropsychiatric symptoms.

Method.

All volunteers submitted to a medical history and physical examination; special emphasis was placed on occupational, smoking, drinking, and

medication histories and the detection of any neurologic or dermatologic signs and symptoms. Physical examinations were performed by three different physicians; each physician's findings were considered final and were not confirmed by a second physician.

The Minnesota Multiphasic Personality Inventory (MMPI)¹⁶ was administered to all employees in a quiet atmosphere at work supervised by management. The only exceptions were a few plant administrators who completed the inventory at home. The individual tests were scored by computer, and the mean and standard deviations were computed for each scale and compared with normative data.¹⁶ In addition, the frequencies of high and low two-point scores were determined.

Each employee, after fasting for at least three hours, was given a bottle of a beverage containing 75 gm carbohydrate (Glucola) to drink. Two hours after ingestion, a blood sample was obtained and the serum glucose and other analyses were performed in an automated clinical laboratory. In persons reporting after 135 minutes, the two-hour serum glucose was considered invalid and not included in the statistical analysis. In addition to the glucose determination, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase, cholesterol, bilirubin, albumin, total protein, blood urea nitrogen (BUN), and hemoglobin values, and an hematocrit reading, red blood cell count, white blood cell count (WBC), serum iron value, and iron-binding capacity were disclosed for each employee.

A routine urine specimen was collected from each volunteer, the pH was adjusted to 7.0, and the specimen was frozen until porphyrin analysis. An attempt was made to shield the urine from ultraviolet light but was not entirely satisfactory in the industrial setting. In addition, each urine sample was analyzed for ALA and PBG by the method of Marver et al¹⁷ and for uroporphyrin and coproporphyrin by the method of Schlenkier et al.¹⁸ The porphyrin and porphyrin precursor levels were expressed per gram of creatinine.

For statistical analysis, employees were subdivided into several different groups according to location in the plant, exposure to chemicals, and educational level. All quantitative results were reported as mean $\pm$ one standard deviation, percent of prevalence, or a correlation coefficient between two variables. Significance was determined by Student's *t*-test or χ^2 test; results reported as nonsignificant are those with the significance level (probability value) of greater than 0.05. Where distribution of

results on a given continuous variable was not normal logarithmic transformations were made before performing *t*-tests or calculating correlation coefficients. Means and standard deviations are always reported as untransformed values.

Results

Descriptive Data.—Seventy-eight persons were studied in the plant. Five women employed in the office were excluded from the analysis. The remaining 73 employees, all men, included one part-time worker and four persons who had not worked in the plant for one to six months. The group of 73 persons was subdivided into four basic occupational subgroups: (1) administrators and technical help, 20 men including engineers, business office workers, laboratory technicians, and janitorial help, all housed in a building separated from the production area and, thus, less exposed to production chemicals; (2) supervisors, 11 foremen spending most of their time in the production area; (3) on-line personnel, 28 persons working in the production area; and (4) maintenance, 14 men with various occupations (plumbers, electricians, etc); some were confined to the maintenance shop and others were frequently in the production area.

As seen in Table 1, the average age of the 18 Negro and 55 white employees was 39.3 ± 11.1 years and the average years of schooling, 11.9 ± 2.6 years. The average duration of employment was 8.3 ± 7.6 years (Table 2). Of 64 workers questioned, 22 missed more than one day from work due to illness in the past year. The average number of days lost for 63 employees was 2.8 days per year. (This excludes one person hospitalized for almost two months with a urinary tract infection.)

Acne.—A specific dermatologic history with special emphasis on acne and porphyria was taken from all the employees and all were examined by one of us (P.P.).

The minimal acne lesion consisted of comedones and inclusion cysts in the temple-zygomatic area and the pinna of the ear. In more severe cases, cysts and comedones were accompanied by pustules on the face and ear, nape of the neck and back, and in the worst cases, the chest and inguinal area. With anatomic spread, the severity of the

lesions and the scarring was generally increased. No erythematous or edematous lesions were found, as previously reported by some investigators studying intense or massive exposures.⁶

"Active acne" was defined as the presence of cysts, comedones or pustules (but not scarring). Each of the three lesions was graded according to the severity (grade 0 to 4) in each location (five possible areas: face, neck, back, chest, and other). The severity grades for each lesion were summed over all five locations. Finally, these severity sums were totaled to produce an overall active acne score (maximal possible score: grade 4 in all five locations = 20 for each of three lesions = 60). This arbitrary rating allowed us to deal with the degree of active acne in a statistical form. Scarring was scored separately by the same system (grade 0 to 4 multiplied by five possible areas = maximal score of 20).

Twenty-five persons had an active acne score of 0 (no lesions), 35 had a score of 1 to 8 (minimal), and 13 employees had a score of 9 or greater (moderate to severe). Scarring was also a highly skewed parameter: 37 employees had a score of 0; 29 had a score of 1 to 8; and 7 had a score greater than 9. As seen in Table 3, with increasing active acne scores, the prevalence of scarring, hyperpigmentation, hirsutism, and complaints of eye irritation was greater.

Another way of expressing the same data is to convert the skewed active acne scores to a more normal distribution by logarithmic transformation (see Methods) and compare these transformed scores with other parameters by correlation coefficients. Scarring, also a skewed parameter, was similarly transformed.

Active acne was correlated with the degree of scarring ($r = 0.80$), the presence of hyperpigmentation ($r = 0.38$) and hirsutism ($r = 0.44$), and complaints about eye irritation ($r = 0.39$). All the above correlations have a significance level of $P < 0.001$. The active acne scores were not significantly correlated with the duration of employment nor with the excretion of coproporphyrins per gram of creatinine.

The occurrence of acne was not significantly greater in Negro employees than in white workers (χ^2 test). Although all six

Table 1.—Distribution, Age, and Educational Level of Employees According to Job Category

Group	No. of Employees	Age*	Years of Schooling*
Administrators, lab technicians, janitors	20	34.0 ± 12.2	13.8 ± 2.3
Supervisors	11	46.8 ± 7.4	12.7 ± 3.0
On-line personnel	28	40.1 ± 10.0	10.6 ± 1.7
Maintenance	14	39.1 ± 10.5	10.6 ± 1.8
Total plant	73	39.3 ± 11.1	11.9 ± 2.6

* Mean ± 1 SD.

Table 2.—Duration of Employment in Plant

No. of Years*	No. of Employees
0-4	33
4-8	10
9-12	1
> 13	29

* Mean ± 1 SD = 8.3 ± 7.6 years.

individuals who stated that they had had teen-age acne and who had worked in the plant for more than 14 months do presently have active acne, the prevalence of acne in this group (100%) was not statistically higher than the prevalence of acne in a group who had also worked in the plant for more than 14 months but had no history of teen-age acne (62% [$\chi^2 = 3.40$; 1 degree of freedom, $0.05 < P < 0.10$]).

The 73 male employees were subdivided into groups with respect to present work location in the plant: TCP formation, 2,4-dichlorophenol (DCP) formation, phenoxyacetic acid production, esterification, formulation and storage tanks, maintenance, supervisory, laboratory help, and administration. Often one man might work in several locations (eg, supervisors might work in both TCP and DCP production and in phenoxyacetic acid production and esterification). In these cases, each area was compared (χ^2 test) to see if the severity of the active acne of the employees might be worse in certain locations in the plant. There were no statistically significant differences, perhaps because of the small size of each group and the mobility of the workers. However, as might be expected, the maintenance men tended to have the most acne (having to clean and repair vats and pipelines) and the administrative people (housed in a separate building) tended to have the least acne.

Mucous Membrane Irritation.—Seven employees complained of itching of the eyes, 14 of frequent tearing, five of "bloodshot eyes," and seven of sties. On physical examination, however, only three (4.1%) had appreciable conjunctival injection. Twenty-three (31.5%) employees had hyperemia of the nasal mucosa and eight (10.9%) had inflammation of the buccal mucosa.

Hyperpigmentation and Hirsutism.—Hyperpigmentation, usually most prominent on the face, consisted of a grayish or brownish tone to the complexion. Hirsutism was most noticeable in the area between the outer edge of the eyebrow and the temple hair margin. Both characteristics were recorded only as being present or absent. As seen in Table 3, 16 subjects had facial hypertrichosis and 30 had hyperpigmentation. Correlation between hirsutism and increased hyperpigmentation was significant ($r = 0.25$, $P < 0.05$). As previously mentioned, hirsutism and hyperpigmentation are significantly correlated with the severity of active acne, but neither is significantly correlated with coproporphyrin excretion.

Urinary Excretion of Porphyrins and Porphyrin Precursors.—The average values of ALA, PBG, and coproporphyrin found in routine urine specimens of 72 workers in the plant are shown in Table 4 along with the normal values from the literature.¹⁰ The excretions of ALA, PBG, or coproporphyrin were not abnormally elevated. One employee, hospitalized several years ago with severe PCT, still has mild uroporphyrinuria (107 $\mu\text{g/gm}$ of creatinine). However, no overt clinical cases of porphyria were found during this study. Only four of the 11 workers with uroporphyrinuria originally described by Bleiberg et al¹⁵ were still working in the plant. Several of the seven employees with uroporphyrinuria who had left the plant had been retested by Dr. Bleiberg before they left and had no elevation in urinary porphyrin excretion.

Several pertinent observations can be made about these urinary porphyrin values. The excretion of ALA and PBG, although not abnormally elevated, nonetheless tended to be relatively increased in the 15 maintenance men versus the other 56 workers. The coproporphyrin excretion per gram of creatinine, although again within normal limits,

was significantly elevated in the maintenance men versus the same 56 workers (48.3 ± 14.4 vs 36.7 ± 19.6 , $P < 0.025$). Persons with higher values for coproporphyrin excretion (≥ 50 mg/gm of creatinine, $N = 15$) did not have any greater duration of employment in the plant than those with lower values (χ^2 test). There was a significant positive correlation between ALA excretion and coproporphyrin excretion ($r = 0.42$, $P < 0.001$) and between ALA excretion and age ($r = 0.42$, $P < 0.001$). There was a significant negative correlation between ALA excretion and serum bilirubin concentration ($r = -0.26$, $P < 0.05$).

Cardiovascular Findings.—Pulse rate and blood pressure recordings were taken. The average pulse was 85.1 ± 10.2 beats per minute; systolic blood pressure, 126.6 ± 12.8 mm Hg; and diastolic blood pressure, 75.4 ± 7.8 mm Hg. Only four persons had a diastolic pressure greater than 90 mm Hg. Cardiac evaluation was unremarkable except for histories of myocardial infarction in three employees.

Pulmonary Findings.—Twenty of 73 employees (27.4%) gave a history of a chronic cough, emphysema, or fairly consistent raising of early morning sputum. Of these 20 workers, 16 (80%) currently smoke cigarettes and the other four (20%) had smoked considerably in the past. In the entire plant, 42 employees (57.5%) currently smoke cigarettes and another 15 (20.6%) gave a history of smoking in the past. The group of current smokers averages 25.6 pack-years.

On physical examination 18 workers were judged to have some impairment of maximal diaphragmatic excursion. Fourteen of these currently smoke and three had smoked in the past. Eight of these 18 workers gave a history of chronic cough or frequent early morning sputum and one gave a history of asthma.

Although the incidence of chronic pulmonary disease in the plant seems to be appreciable, it cannot be attributed to any industrially related cause, as suggested by the report of Bauer⁷ because 78% of the employees now smoke or have smoked cigarettes previously.

Hepatic Function.—All serum total bilirubin values and albumin concentrations were within the normal laboratory range (Table 5

includes mean values). Two subjects had alkaline phosphatase values slightly above the normal laboratory range (18.7 and 19.0 King-Armstrong units/100 cc, respectively [normal range, 7 to 18 King-Armstrong units/100 cc]); the other liver function tests were normal. Two employees had SGOT levels elevated above the normal range (48 and 121 Karmen units/ml, respectively [normal range, 7 to 45 Karmen units/ml]), but otherwise had normal liver function tests. The employee with an SGOT value of 48 Karmen units/ml was receiving lincomycin injections at two- to four-week intervals. The SGOT value of 121 Karmen units/ml was not confirmed by a second testing, and the subject had no other evidence of liver malfunction. Six persons had palpable liver edges; five of these six findings were observed by one of the three physicians. Two of these six subjects were heavy beer drinkers (at least four cans of beer per day), and one had emphysematous lung changes with lowered diaphragm. Only one of the six subjects with a palpable liver had an abnormal liver function test, an alkaline phosphatase level of 19 King-Armstrong units/100 cc.

Gastrointestinal Results.—Several studies of 2,4,5-T workers have mentioned high prevalences of anorexia and weight loss, postprandial flatulence, nausea and vomiting, abdominal pain, and documented cases of gastritis and ulcers.^{4,6-8,10} At the time of the examination 22 workers in this plant (30%) were intermittently experiencing at least one of the following symptoms: nausea, vomiting, diarrhea, abdominal pains, or blood in the stool. Two persons in this group and four other persons had a history of "ulcers" (6 of 73 persons or 8.2%). We found no results from other industrial settings with which to compare our data.

Neurologic Findings.—Several authors have noted lower extremity weakness and fatigue in many of the patients with chloracne in 2,4,5-T factories.^{4,7} Only seven of 73 (9.6%) employees in our study complained of lower extremity fatigue or difficulty in climbing stairs. Five of these workers gave a history of arthritis in the lower extremities or heart disease with dyspnea; thus, only two (2.7%) experienced leg fatigue totally unexplained by other concomitant disease. Lower extremity weakness was not detected

in the neurologic examination of any subject.

Eight workers (11%) complained of nonspecific headaches. Ten workers had decreased auditory acuity (inability to hear a watch ticking 1 cm from the ear); four of these had tympanic membrane disease. No discrimination was made between nerve or bone conduction defects. A decrease in olfactory discrimination was observed in only one employee and was most likely due to nasal obstruction. Two persons had a decreased sense of proprioception (one with history of chronic lumbar arthralgia secondary to traumatic injury to the back). In three persons, Achilles tendon reflexes were absent without other neurologic deficits (one had a two-year history of diabetes mellitus). Tremors of the hands were observed in three employees. We found no abnormalities of cranial nerves other than those noted above: no clonus, no alterations in deep tendon reflexes of musculi biceps or triceps brachii or quadriceps femoris, and no alteration in pain sensation.

Results of Other Laboratory Determinations.—Only one employee had an elevated BUN value, as shown in Table 5 (29 mg/100 ml; normal range, 6 to 24 mg/100 ml), and none had an elevated uric acid level (normal range, 3.0 to 7.9 mg/100 ml). The serum cholesterol (normal range, 133 to 294 mg/100 ml) was elevated in seven of 71 persons. There was an unexplainable elevation in the serum LDH (normal range, 50 to 160 Wacker units/ml) in 20 of 70 employees (28.6%); this may have been due to centrifuging clinical chemistry blood specimens more than two hours after sampling.

The two-hour serum glucose levels, as determined by the automated ferricyanide method for glucose determination, were judged satisfactory with 58 employees (see Methods). Six employees (10.4%) had a two-hour serum glucose value of ≥ 140 mg/100 ml²⁰ after a 75-gm oral carbohydrate load (145, 148, 152, 171, 174, and 176 mg per 100 ml). The average age of these six individuals (50.6 years; range, 39 to 62)

Table 3.—Distribution of Certain Signs, Symptoms, and Test Scores Among Three Categories of Active Acne Severity

	Active Acne Score		
	0	1-8	≥ 9
No. of employees			
Hirsutism	3/25 (12%)	4/35 (11%)	9/13 (69%)
Hyperpigmentation	5/25 (20%)	15/34 (44%)	10/12 (83%)
Scarring	1/25 (4.0%)	22/35 (63%)	13/13 (100%)
Eye irritation (history of tearing, itching, sties, bloodshot)	1/25 (4.0%)	8/35 (23%)	6/13 (46%)
Mean score of Mania scale of MMPI	55.4 $\pm$ 7.7	58.8 $\pm$ 10.2	64.9 $\pm$ 10.5*

* The persons with acne scores of > 9 had significantly higher scores on the Mania scale on the MMPI ($P < 0.05$).

was higher than that of the 52 individuals whose results were < 140 mg/100 ml (39.3 years; range, 21 to 56). One of the six was the only known diabetic in the plant; he had a 19-year work history in the plant and a two-year history of diabetes which is currently being treated with tolbutamide. The average period of employment in this plant for the six individuals was 9.2 years, with the range being 1 to 19 years; three had minimal chloracne and one had severe chloracne. None of the six had a family history of diabetes; one was obese. The prevalence of 10.3% hyperglycemic results in this factory is consistent with a 14% prevalence figure of two-hour postglucose hyperglycemia in a random sample of a normal population in Bedford, England.²¹

Only two of 72 employees had a hemoglobin value of less than 13 gm/100 ml of blood, and 16 employees (22%) had a serum iron determination of less than 75 μ g/100 ml. The mean serum iron value was 97 ± 32 μ g/100 ml and only two employees had a value of 160 μ g/100 ml or greater. The average value for saturation of the iron-binding capacity was $27.4\% \pm 9.0\%$, with 27 persons (37%) having a value of less than 25%. Seven persons had a WBC of less than 5,000 cells/cu mm, but it was 4,000 cells/cu mm or less in only two employees. None of the seven had an absolute granulocytopenia ($< 1,500$ neutrophils/cu mm)²² and only one worker had a lymphopenia ($< 1,000$ lymphocytes/cu mm).²² Since the normal hematologic values used here are the 95% confidence limits of a study of a normal population,²² single cases of granulocy-

Table 4.—Urinary Porphyrin Excretion

Test	Plant Values, μg/gm of Creatinine*	Normal Values ¹⁹	Upper Limit of Normal, μg/gm of Creatinine
ALA	1,021 ± 406	1,900 ± 600 μg/gm creatinine	3,100
PBG	444 ± 237	700 ± 400 μg/gm creatinine	1,500
Coproporphyrin	39.3 ± 19.0	0.175 μg/liter	175†
Uroporphyrin	Trace†	0.15 μg/liter	15‡

* Mean ± SD, N = 72.

† Measurable in only one person; value, 107 μg/gm of creatinine.

‡ Values derived from normal by assuming a 70-kg man excretes creatinine at ≥ 1.5 gm/day and 1,500 ml of urine.

topenia and lymphopenia would not be unexpected in a population of 73. The red cell morphology and platelet count, determined by scan of the peripheral blood smear, were normal in all subjects.

MMPI Results.—The MMPI scores of production workers (including on-line personnel, supervisors, and maintenance men [N = 52]) and the administrative staff (including laboratory technicians [N = 17]) were analyzed separately because of the difference between the two groups in environmental exposure and educational level. Four janitors, currently working in the administration building, were eliminated from the analysis of the administrative staff because of a different educational background and previous exposure as production workers.

MMPI results are based on an analysis of scores of all subjects on 13 separate scales. Ten of these scales are designated by common clinical terms and are thus somewhat self-explanatory (Table 6). Detailed descriptions of each scale are found in *An MMPI Handbook*.¹⁰ The remaining three scales, the L, F, and K scales, measure the validity of the test results as an accurate profile of the subject. A high L score indicates that the subject answered most questions according to socially desirable standards rather than according to individual preferences. More highly educated subjects tend to have lower L scores; this is consistent with our finding of significantly lower L scores in the administrative staff. A high F score may be obtained if a subject answers in a prankish way, if he has a poor ability to read or comprehend the items, or if he is severely mentally disturbed. Since only one subject out of 69 had a high F score (F > 76), the test seems to have been both understood and taken seriously by the workers. A high K score indicates a high degree of

defensiveness in a person (an unwillingness to admit that he differs in any respect from what he considers normal); this score increases with educational level. The mean K scores for both groups in this plant are normal for their educational levels and do not significantly differ from each other.

The only significant differences in means on all scales between administrative staff and production workers were on the L and Hypochondriasis scales, with the production workers presenting a more hypochondriacal picture than the administrative staff. When scores of both groups of employees were compared with the normal values given for the MMPI test scales (N, approximately 300; mean, 50; standard deviation, 10), administrative staff and production workers varied significantly from normal on a total of six and nine scales, respectively (Table 6). The normal values for the MMPI, however, were based on scores of a small population of Minnesota males who took the test just before World War II.¹⁶ Since many obvious demographic differences exist between the plant population and the "normal population," it was thought that a more meaningful definition of the plant population would be obtained by searching for personality patterns appearing in high frequencies within the plant. A high-point code system was used which grouped subjects according to the two scales in which they scored the highest. The following high-point codes had the greatest frequency (F): administrative staff, hypomanic-hysterical, f = 23%; production workers, hypomanic-psychopathic, f = 12%. It is apparent from these small frequencies that no one personality pattern tended to dominate either administrative or productive group.

Correlation coefficients were calculated

for several MMPI scales with other parameters, such as porphyrin excretion, chloracne, job history, and several biochemical tests. A significant correlation was found between the score of severity of active acne and the hypomanic scale ($r = 0.33$, $P < 0.01$). Furthermore, the mean manic scale score for the group with the most severe chloracne was significantly higher than the means of the two groups with less severe acne ($P < 0.05$ [Table 3]).

Comment

Acne.—Forty-eight of 73 (66%) employees in our study had some degree of acne, but only 13 (18%) had moderate to severe lesions. Most previous investigations of acne occurring in workers in 2,4,5-T plants have selectively presented clinical and pathologic findings in those severely affected. In contrast, the present study surveyed the prevalence of acne in the entire employee population and found the acne absent or minimal in 82% of the workers.

The severity of active acne correlated with the presence of scarring, hyperpigmentation, hirsutism and complaints about eye irritation (Table 3). Dugois et al¹⁰ reported a 50% incidence of conjunctivitis in 2,4,5-T workers with acne. Although we had many complaints about eye irritation, only three workers were observed to have conjunctivitis. However, 23 (32%) of the employees had hyperemia of the nasal mucosa and eight (11%) had hyperemia of the buccal mucosa.

Our findings that the presence of hyperpigmentation and hirsutism correlate quite significantly with the severity of acne and not at all with coproporphyrin excretion suggests that these two signs, which are usually thought of as part of the PCT syndrome, may be more closely related to chloracne in 2,4,5-T plants. Other studies support this view, such as (1) the findings of Bleiberg et al¹⁵ that the presence of hirsutism and hyperpigmentation correlated better with

Table 5.—Clinical Laboratory Data

Test	Mean	SD	N*
BUN (mg/100 ml)	14.5	3.9	72
Uric acid (mg/100 ml)	5.4	1.0	72
Cholesterol (mg/100 ml)	237	44	71
Two-hour serum glucose (mg/100 ml)	95	32	58†
Alkaline phosphatase (King-Armstrong units)	11.2	2.5	71
LDH (Wacker units)	146†	46	70
SGOT (Karmen units)	22	13	71
Bilirubin (mg/100 ml)	0.44	0.16	71
Albumin (gm/100 ml)	4.6	0.3	71
Hemoglobin (gm/100 ml)	14.9	1.1	72
Serum iron (μg/100 ml)	97	32	70
Total iron-binding capacity (μg/100 ml)	348	44	69
Saturation of iron-binding capacity (%)	27.4	9.0	69
WBC (cells/cu mm)	7,160	2,190	72

* Variation in N secondary to sampling difficulties; for N = 73, mean age $\pm$ SD = 39.3 ± 11.1 ; 25% of population are Negroes, 75% are white.

† For N = 58, mean age $\pm$ SD = 39.3 ± 10.9 ; 29% of population are Negroes, 71% are white.

‡ Elevated value is probably due to poor sample handling.

the presence of chloracne than with uroporphyrinuria, and (2) the findings of other studies of 2,4,5-T factories^{7,23} in which workers were noted to have chloracne and hyperpigmentation but no mention was made of skin fragility, vesicular eruptions, or red urine.

As stated in the introduction, Kimmig and Schulz¹⁻⁶ have demonstrated the potent acnegenic properties of TCDD, an unwanted side product in the synthesis of 2,4,5-T. There is a tendency in the plant we studied for the maintenance men, who have the most direct exposure to all products of synthesis, to have the most severe acne and for the administrative personnel, who have the least exposure, to have the least acne. However, an association of a higher prevalence of acne with any particular location in the plant could not be demonstrated, eg, in the TCP synthetic area where one would expect TCDD concentration in the environment to be the highest. The plant has taken steps to decrease the contamination of the TCP end product by dioxin, and the concentration of the contaminant in the TCP has dropped from 10 to 25 ppm to 1 ppm (see the following subsections on chemistry and the plant). At the time of the study the effect of the safety measure to decrease contamination on the severity or prevalence of chloracne in the factory could not be evaluated since (1) there were no previous prevalence

Table 6.—Scale Scores on the MMPI

Scale	52 Production Workers			17 Administration Workers		
	Mean	SD	P*	Mean	SD	P*
L	52.5	8.2	NS	46.1	5.8	NS
F†	54.6	7.4	<0.0025	54.4	8.8	NS
K	53.2	8.9	<0.025	55.4	6.3	<0.025
Hypochondriasis‡	55.5	9.8	<0.00025	48.8	8.5	NS
Depression	59.5	11.2	<0.0001	56.7	11.5	<0.01
Hysteria	59.0	8.8	<0.0001	58.9	6.7	<0.001
Psychodeviance	59.8	12.1	<0.0001	55.5	12.1	<0.025
Masculinity	57.4	7.6	<0.0001	60.7	6.1	<0.00025
Paranoia	52.9	8.3	<0.05	52.6	9.6	NS
Psychasthenia	52.1	10.4	NS	50.8	8.9	NS
Schizophrenia	51.2	9.8	NS	51.2	10.0	NS
Mania	60.0	9.0	<0.0001	56.8	12.4	<0.01
Social introversion	51.4	8.4	NS	50.1	9.8	NS
Years of schooling	10.9 ± 2.1			15.2 ± 1.5		P 0.001‡
Coproporphyrin excretion, µg/gm of creatinine	38.8 ± 16.0			37.9 ± 24.7		NS§
No. of persons with some degree of acne	36/52			10/17		NS
Active acne score	6.2 ± 9.6			2.5 ± 3.2		NS§

* Significance values by Student's t-test, comparing the above populations to the normal population as defined in the text of the results.

† The two plant groups are significantly different ($P < 0.005$). This would be expected on an education basis.

‡ The two plant groups are significantly different ($P < 0.01$).

§ Significance by Student's t-test.

|| Significance by χ^2 test.

figures on chloracne in the plant with which to compare and (2) the effect of such a measure on the severity or prevalence of a chronic disease such as chloracne may take longer than six months to become evident.

Individuals seemed to vary greatly in their susceptibility to acquire chloracne. This observation is consistent with (1) the lack of correlation between the duration of employment in the plant and the severity or presence of chloracne and (2) the tendency toward an increased susceptibility to chloracne in persons with history of teen-age acne.

Chemistry.—Although the structures of 2,4-D and 2,4,5-T (Figure) differ only by one chlorine, the commercial syntheses of the two compounds are dissimilar. The starting product for 2,4,5-T is 1,2,4,5-tetrachlorobenzene which reacts with methanol and aqueous sodium hydroxide to form 2,4,5-trichlorophenolate, 2,4,5-trichloroanisole, and small amounts of several unwanted side products, eg, TCDD. The reaction product is steam-stripped to remove the anisole. At this point, sampling of various batches shows

the TCDD to be present in 10 to 25 ppm. About six months before our survey, the company installed a device which removed most of the TCDD. The TCP thus produced contained less than 1 ppm TCDD.

The TCP reacts with monochloroacetic acid (MCA) to form 2,4,5-T. The latter is esterified with various alcohols or allowed to react with dimethylamine, and then formulated and packaged. Some 2,4,5-T and 2,4-D is sold as the unesterified acid in solid form.

The starting materials for 2,4-D are phenol and chlorine (gas) which react in an exothermic process to form DCP. Subsequent reactions with MCA to the phenoxyacetic acid are similar to 2,4,5-T. In 2,4-D production there is no formation of the TCDD.

The Plant.—The plant employs several measures in an attempt to improve industrial hygiene. Clean work clothes are issued daily, and separate lockers for street and work clothes are provided. All production workers said they showered daily before leaving the plant. The DCP and TCP are made in one building and the 2,4-D and 2,4,5-T (acids) and their esters in another. Attempts have been made to improve ventilation, and recently the company has been successful in removing most of the TCDD before the TCP leaves the area in which it is synthesized. A dermatologist employed by the company visits the plant at least weekly, largely to treat the chloracne.

Almost all operations are carried out in closed processes (eg, tank car to pipeline to reaction vessel to next pipeline to next reaction vessel). There is of course some leakage, and frequently men working in maintenance must clean the inside of the reaction tanks or open pipelines.

Porphyria Cutanea Tarda.—A large outbreak of PCT in Turkey in 1956 due to the accidental ingestion of hexachlorobenzene²⁴⁻²⁸

plus the high prevalence of PCT described by Bleiberg et al¹⁵ in this 2,4-D and 2,4,5-T plant in 1964 support a direct toxic etiology of many cases of PCT. The actual etiologic agent of PCT in this plant is unknown. We have administered reagent grade DCP to rats and observed an increase in the urinary excretion of coproporphyrin (unpublished data). A single oral dose of DCP caused a threefold increase in the activity of hepatic ALA synthetase, the rate-limiting enzyme in porphyrin biosynthesis. Rimington and Ziegler²⁰ reported a series of structurally similar chlorinated benzene compounds which caused experimental porphyria in rats. The TCDD, because it is a potent hepatotoxin and acnegen, was not examined for its ability to cause porphyria in experimental animals.

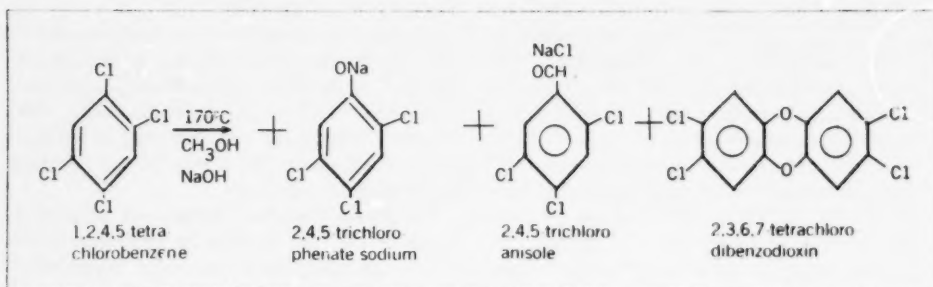
In the report of Bleiberg et al¹⁵ in 1964 of this same plant, 11 employees had uroporphyrinuria and several had hirsutism, hyperpigmentation, or skin fragility, or all three. In the three case histories presented, two patients had vesicular eruptions on exposed areas of the body, two had hepatic dysfunction, and the tissue obtained from the two reported liver biopsies fluoresced intensely with ultraviolet irradiation. These three case histories unquestionably fulfilled the criteria for the diagnosis of PCT.

Our reexamination of the same plant six years later revealed no clinical PCT; only one employee had mild persistent uroporphyrinuria. The reason for the decrease in severity and prevalence of PCT in this plant is unknown. Possible reasons include (1) increased encouragement of personal safety habits of workers, and (2) decrease in the contamination of PCT by the hepatotoxin, TCDD, and perhaps simultaneously by porphyrogenic chemicals.

Porphyria cutanea tarda (ie, uroporphyrinuria, skin fragility, and vesicular eruptions on the skin) does appear to be a symptom-complex distinct from that of chloracne (ie, cysts, pustules, comedones, and scarring of the skin); both were found in workers in this plant in which 2,4-D and 2,4,5-T are manufactured. The independence of these syndromes is supported by (1) the lack of correlation between the severity or even presence of chloracne and uroporphyrinuria in the previous study,¹⁵ and (2) the persistence of chloracne in the factory six years later, despite the disappearance of the uroporphyrinuria and skin fragility. Even if the etiologic agent is the same, the syndromes apparently can occur independently and certainly have different clinical courses.

The statistically higher coproporphyrin excretion in the maintenance men suggests that they have a higher toxic exposure; they also have a tendency towards more severe acne. These men repair the inside of reaction vessels and leaking pipelines, and although their exposure is sporadic, it is apparently more intense.

Recently, much attention has been directed towards the finding of hemosiderosis and hyperferremia in patients with PCT, often in those with an alcoholic history.³⁰⁻³² Although studies of iron metabolism were not reported in the patients with hexachlorobenzene intoxication, chelating agents did appear to reverse the clinical symptoms and porphyrin excretion.³³ In our study, despite the absence of uroporphyrinuria in the workers at the present time, a tendency towards hyperferremia might be expected. On the contrary, we found an unexplainable trend towards hypoferremia and a lower iron-binding saturation, with little demonstrable anemia.



Hepatotoxicity.—TCDD, which has been incriminated as a potent acnegenic agent, is also very hepatotoxic. A single oral dose of 0.05 to 0.1 mg/kg to rabbits resulted in death in one to two weeks. Autopsy revealed extensive necrosis and enlargement of the livers.⁵ Similarly, dermal application of the tarry residues in 2,4,5-T synthesis caused gross hepatic lesions and rapid death in guinea pigs.¹⁰ Clinically, several investigators have looked for evidence of hepatotoxicity in 2,4,5-T-plant workers affected with chloracne. Bauer et al⁷ noted that two of nine cases had slightly delayed sulfobromophthalein excretion and three had abnormal liver biopsies. In the report of Bleiberg et al¹⁵ of patients with chloracne and porphyria, two subjects had hepatic dysfunction and two had abnormal liver biopsies. Dugois and co-workers^{8,10} have noted hyperlipemic and hypercholesterolemic sera in their subjects. Hofmann and Meneghini²³ found no hepatic damage in six patients with chloracne. Of the liver tests performed in this study (bilirubin, albumin, SGOT, and alkaline phosphatase), only four values were elevated. Three of these four elevations were extremely mild, and the fourth was accompanied by no other abnormal liver test values. Of the six patients with palpable livers, only one had a mildly elevated liver function test. Although TCDD and other chemicals produced in 2,4,5-T synthesis may be hepatotoxic in humans, the prevalence of demonstrable chemical liver dysfunction in this plant is minimal.

Systemic Toxicity.—As noted in the introduction, a variety of other signs, symptoms, and laboratory findings have been noted in various studies of 2,4,5-T workers with acne. We found no unexplainable significant increases in abnormal function of cardiovascular, pulmonary, intermediary metabolic, or hematologic systems in comparison with normal populations. Although the prevalence of gastrointestinal complaints seems high (30%) and although physical examination revealed occasional unexplainable neurologic deficits (decreased hearing, six of 73 subjects; diminished proprioception, one of 73; absent ankle jerks, two of 73), we could find no figures of comparable studies with which to compare; hence, a judgment on the normality or abnormality of the prevalence

of these findings in this population would only be conjectural.

MMPI.—The MMPI results are important in that they offer an objective profile of the workers in one herbicide synthesizing plant. Conclusions about personality changes secondary to chronic exposure in a plant in which 2,4-D and 2,4,5-T are manufactured can only be tenuous, however, because we have no suitable group with which to compare these results. The comparison of MMPI results of these factory workers with the normal population of pre-World War II, white subjects from Minnesota was inescapable since the scoring system for the test is based upon this "norm."¹⁶ Nonetheless, we consider these groups incomparable. The only evidence to suggest any environmental effect of this herbicide plant on personality is the significant correlation between severity of chloracne (a known toxic effect) and the score on the hypomanic scale. This is an interesting finding and somewhat contradictory to the apathy and psychomotor retardation reported by Bauer et al.⁷

Many previous investigations of both acute and chronic poisoning in 2,4,5-T plants have reported the symptoms of anorexia with weight loss, fatigue, debility, and asthenia.^{4,7} However, only one author has described in detail personality changes thought to be associated with chemical exposure. Bauer et al⁷ studied nine workers with severe chloracne which still persisted five years after termination of their exposure in a 2,4,5-T plant and described a syndrome of general weakness, fatigue, apathy, and decreased libido alternating with fits of anger and irritability. Rorschach tests showed a weakened emotional reaction, a lack of concentration, slowed thought processes, and perseveration. This whole syndrome was designated by the term "psychovegetative disorder."

The inconsistency of our finding of a significant correlation between hypomania and chloracne and the previous description of lethargy, dulled emotional response, and apathy⁷ remains to be adequately explained. Possible reasons include a basic difference in methodologies and a difference in testing period with relation to the time of exposure. Additionally, the severity and chronicity of the organic disease in subjects studied by

Bauer et al⁷ may have induced personality changes which masked any manic effects found with less severe disease.

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Jacob Bleiberg, MD, gave permission for entry of the factory studied and provided written records of past medical histories for comparison on some workers.

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Measurement of the Exposure of Workers to Pesticides*

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There is not a single pesticide for which the interrelationships between occupational exposure by different routes, the fate of the compound in the human body, and its clinical effects are all adequately known.

Results of the direct measurement of exposure to pesticides may be used in evaluating the relative hazard of different routes of exposure, different operational procedures, and different protective devices. Results of the indirect measurement of exposure may be of use for the same purpose; in addition, these indirect measures may be used in relating exposures under observed conditions to clinical effects.

This paper describes and evaluates detailed procedures for the use of air samples, pads, and washes in the direct measurement of the dermal and respiratory exposure of workers to pesticides. Good methods are not available for measuring oral exposure. Any measure of the absorption, storage, physiological effect, or excretion of a compound constitutes an indirect indication of exposure to it.

The importance of insects as vectors of disease, as pests, and as destroyers of crops has long been recognized; and the necessity for their control has led to the development of increasing numbers of new pesticidal agents. There are some inevitable hazards that accompany the use of these toxic materials. Each year many deaths and many more illnesses, of varying degrees of severity, are attributed to pesticides. Some of the newer organic phosphorus compounds, particularly parathion, and a few of the chlorinated hydrocarbon materials, such as dieldrin, have caused occupational poisoning. Such incidents are usually the result of accident, use of the materials in a careless manner, or neglect or inability of workers to wear adequate protective clothing.

In order to evaluate the health hazard involved when working with these toxic compounds, it has been of value to determine the amount of exposure that workers undergo while carrying out various jobs related to the use of pesticides. A number of methods have been developed for measuring the

exposure of workers and others to these agents. These methods may be divided conveniently into, first, the direct methods of measurement and, secondly, the indirect methods.

The direct methods involve the use of some mechanism to trap the toxic material as it comes in contact with the workman during his exposure period. The amount of trapped toxicant, as determined by chemical analysis, bio-assay, or other methods, is then a direct measure of the particular exposure being measured. The indirect methods involve the measurement of some effect of the toxicant upon the exposed individual.

Although a number of papers on the exposure of workers to insecticides during spray operations have appeared in the technical literature, no discussion of the various methods available or evaluation of their efficiency has been published. There are three routes of exposure to be considered: respiratory, dermal, and oral. The present paper reviews in detail the methods available for direct measurement of the exposure of workers to pesticides and summarizes the results obtained by the application of these methods in specific situations. A less comprehensive coverage is given to the indirect methods, since these procedures are already more familiar to investigators in this field.

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DIRECT METHODS

RESPIRATORY EXPOSURE

Respiratory exposure cannot be separated completely from oral or from dermal exposure in the sense that some material retained on the mucous membranes of the upper respiratory tract will be absorbed through these membranes or swallowed and made available for absorption by the gastrointestinal tract. However, the error is on the side of greater safety if all inhaled material is assumed to represent respiratory exposure, since most, if not all, materials are absorbed more rapidly and more completely through the lungs than through the skin and, for this and perhaps other reasons, are more toxic by the respiratory route.

Estimation of respiratory exposure from air concentration

Respiratory exposure has been estimated most commonly by measuring the concentration of the toxicant in the air. This estimate is probably valid for true gases or vapours, but when particulate matter is involved, the lack of homogeneity in the atmospheric concentration leaves such a calculation open to question. It is practically impossible to duplicate mechanically the aerodynamics of inhalation and exhalation through a pliable nostril. Generally the tidal character of respiratory air flow has not been taken into account in taking air samples. Frequently, even the relation of air velocity in the intake of the sampler to air velocity (minimal, maximal, or average) in the nares has been ignored. The fact that the nares are normally directed downwards and cannot receive free-falling particles is usually neglected.

The adequacy of estimates of respiratory exposure based on air concentration values depends in part upon how well the sampling device collects the same spectrum of particle sizes as is picked up by the nostrils in breathing. The midjet impinger (Culver et al., 1956) has been used for air sampling and has been reported to duplicate reasonably well this spectrum of particle sizes. The Greenburg-Smith impinger (Hatch et al., 1932) has the advantage of sampling a larger volume of air in a given time and therefore improves sensitivity where the concentration of toxicant is low or the duration of a particular exposure is brief. Caplan et al. (1956) compared the Greenburg-Smith impinger and an all-glass fritted absorber and found the absorber about four times as

efficient for measuring malathion aerosol as the impinger.

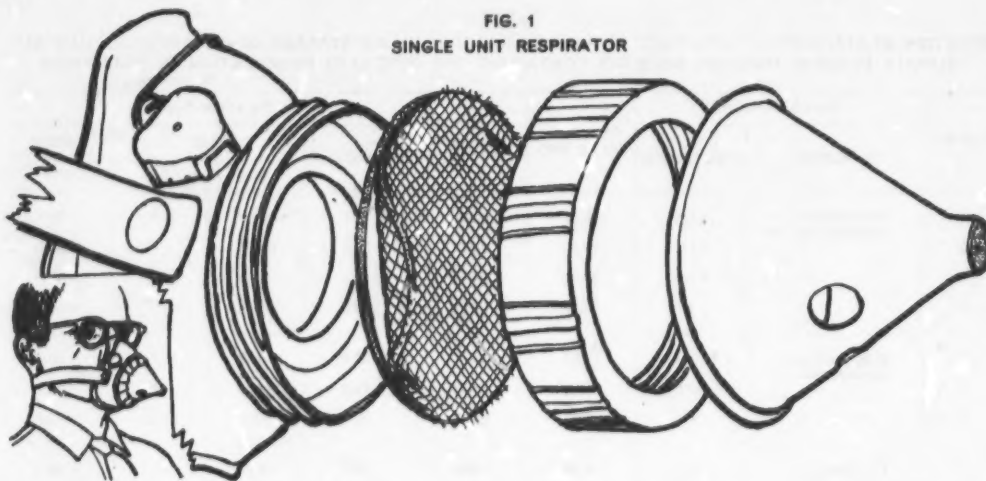
A satisfactory method for collecting air samples for determination of parathion content involves a modified Greenburg-Smith impinger arrangement, using three 500-ml impingers connected in series. Ethyl alcohol is used as the solvent, with 250 ml in the first impinger and 100 ml each in the second and third. Although the efficiency of this arrangement for removing parathion vapour is questionable, it is quite effective at removing the particulate form. All connexions should be of glass or synthetic rubber, since natural rubber connexions give rise to an interference in the chemical analysis. The glass assembly can be prepared by bending and sealing Pyrex glass ball joints, size 28/12, to 500-ml Greenburg-Smith dust-sampling impingers. This arrangement can be attached to a 12 inch $\times$ 22 inch (about 30.5 $\times$ 56 cm) plywood panel with adjustable clamps to hold the glass parts and a 12 inch $\times$ 12 inch (about 30.5 $\times$ 30.5 cm) base used to hold the arrangement upright. The ball joints themselves are lubricated with silicone vacuum grease and held together with clamps designed for the purpose.

While taking air samples to be used in calculating respiratory exposure, the intake tube of the sampler unit should be positioned so that the opening is pointed downwards and is approximately at nose level for a person of average height. The orientation with regard to height is especially important when taking samples indoors, where walls or ceilings are being sprayed.

Suction may be provided by an electrical vacuum pump or, for field use where electricity is not readily available, by a hand-turned pump, a gasoline-engine-driven pump, or a Venturi tube operated by compressed carbon dioxide (Wolf et al., 1959). The flow produced by a given pump in conjunction with a particular sampling device may be calibrated in advance to avoid the necessity of carrying a gas flow meter into the field. In general, air flow rates of from 0.5 to 2.5 cubic feet (14.2 to 70.8 litres) per minute have been found most reliable when using 100-250 ml of solvent in the impingers. Meters are necessary while using compressed gas and a Venturi tube as a source of vacuum, because the flow of gas is somewhat irregular.

When the primary objective in air sampling is recovery of the vapour form of a compound, a

FIG. 1
SINGLE UNIT RESPIRATOR



The filter pad used for dust is made by stapling 32 layers of surgical gauze to an alpha-cellulose respirator pad (shown partially separated). This pad is held in place by the retaining ring, while the plastic funnel is attached by tape. The complete assembly is shown at the lower left of the illustration.

different sampling method must be employed. Tests of efficiency in removing parathion vapour were conducted with traps utilizing glass wool, alumina (80-200 mesh adsorption alumina), Florisil, and dry-ice-acetone. These tests showed the alumina column to be the most satisfactory. The alumina column not only adsorbed a high percentage of the parathion but also enabled the adsorbed parathion to be eluted easily from the adsorbent by the use of acetone or 95% ethyl alcohol. The alumina column has also been found to be satisfactory for trapping vapour of γ -BHC (Hornstein & Sullivan, 1953).

After determination of the concentration of toxicant in the air, the respiratory exposure of exposed individuals can be calculated by using an assumed tidal volume and respiratory rate. The average values for lung ventilation in man as given by Spector (1956) are 444 litres per hour during rest, 1740 litres per hour during light work, and 3600 litres per hour during heavy work. An even more accurate calculation can be made if lung ventilation is actually measured under the conditions of work being studied.

Direct measurement of respiratory exposure

A different approach to the estimation of respiratory exposure (Batchelor & Walker, 1954) enables the subject himself to provide the air flow, thereby avoiding several complications mentioned above. The method involves determination of the amount of

toxicant deposited on the outer absorbent or filter pads of the respirator worn by the subject, during an accurately-timed period of exposure. If a properly fitting face-piece is used, all inhaled air must pass through the pads so that total volume does not have to be measured or estimated. By restricting the size of the aperture through which the air must flow before it reaches the respirator pad, it would appear possible to reproduce quite well the aerodynamics of the air flow through the nostrils themselves. Edson¹ has provided a metal snout to protect the respirator pad from direct spray impact. Though he does not describe the snout, it apparently did not serve as a restrictive aperture.

The present authors, after working with several preliminary designs (double-unit respirators, glass funnels, etc.), selected a single-unit respirator and a modified plastic funnel for giving protection from direct spray impact and also for restricting the size of the aperture. The stem of the funnel is shortened and plugged with cork, and two holes, 12 mm in diameter and 6 mm apart, are drilled midway between the base and the apex. The modified funnel has approximately the same greatest diameter as the threaded retaining ring of the respirator, to which it is taped securely with the holes directed downwards during use. Fig. 1 shows an expanded view of the

¹ Edson, E. F. (1956) Unpublished report of the Medical Department, Fison's Pest Control Ltd.

TABLE 1
RETENTION BY RESPIRATOR FILTER PADS OF PARATHION BORNE ON AIR STREAMS OF INDICATED VOLUME AND VELOCITY PASSING THROUGH BUBBLERS CONTAINING THE INDICATED FORMULATION OF PARATHION

Trial No.	Parathion source		Air volume (cubic feet)	Air velocity (cubic feet per minute)	Test pad (μ g)	Parathion found		
	Formulation	g/100 ml water				Trap		Fraction retained on test pad (%)
						1 (μ g)	2 (μ g)	
1	25 % Water-wettable powder	0.120	8.45	0.352	58.1	trace	— ^a	> 92.1
2		0.120	14.20	0.592	83.2	trace	— ^a	> 94.3
3		0.120	32.40	0.661	147.7	9.0	trace	> 91.3
4		0.340	63.00	0.656	266.0	15.5	16.4 ^b	> 89.3
5	45 % Emulsion concentrate	0.068	14.50	0.604	32.9	trace	— ^a	> 86.8
6		0.068	30.50	0.953	41.3	trace	— ^a	> 99.2
7		0.350	32.20	0.671	49.7	10.0	trace	> 76.8
8	1 % Dust	—	8.50	0.654	53.5	trace	^c	> 91.5
9		—	14.50	0.604	364.5	7.4	^c	> 98.0

^a Second trap was combined with first for analysis.

^b Reddish colour obtained, indicating questionable determination.

^c Value obtained was below experimental limit of chemical method.

equipment and a detail of the assembly as worn. Material deposited on the inside surface of the funnel, as well as material deposited on the pad, is removed by a suitable solvent and measured.

The necessity of using some sort of cover to prevent impingement on to the respirator pad has been shown in studies of workers using dinitro-ortho-secondary-butylphenol (DNOSBP).¹ Analysis of 16 uncovered respirator pad samples showed an exposure of 0.47 mg per hour. Concurrently, a group of ten samples was collected from respirators that were worn loosely over the face and plugged to prevent air flow through the filter. Analysis of these pads showed an exposure of 0.36 mg per hour. These results indicate that, using an uncovered respirator, about 75% of the apparent respiratory exposure was actually due to impingement.

Respirators that are equipped with only filter pads for the purpose of measuring toxic materials should not, of course, be used even for short periods of time as a replacement for respirators equipped with chemical cartridges under conditions where exposure without the cartridges would be even slightly hazard-

ous to the wearer. In such cases, the cartridge type of respirator should be worn, and the measurement of toxic material should be taken from filter pads installed in front of the cartridge and behind the plastic funnel.

Tests have been conducted to determine whether or not the filter pads used for measuring respiratory exposure were an efficient trap for parathion. A measured quantity of air was drawn at a known rate through a closed system containing three elements: a source of parathion (water-wettable powder in water, water emulsion, or a 1% parathion dust), the test filter pad, and two alumina traps (described above) to retain any parathion vapour passing through the test pad. The latter two elements were analysed for parathion content by the method of Averell & Norris (1948). The air velocity was set at about 0.6 cubic feet (17.0 litres) per minute to approximate the inspiration rate of normal breathing. The results of these tests are presented in Table 1.

It is apparent that the filter pads were quite efficient in retaining the parathion vapour. The retention by the pads varied from > 77% to > 98% with a mean of > 90%. Quantities of parathion less than 5 μ g cannot be measured accurately and are

¹ Wolfe, H. R., Durham, W. F. & Batchelor, G. S. Manuscript in preparation.

reported as "trace." However, these amounts are considered to be 5 μg in calculating the parathion-retaining efficiency of the pad. There is some indication that parathion vapour from dust and water-wettable powder formulations may be retained on the pad somewhat better than that from emulsifiable concentrate formulations. These results indicate that under conditions of testing normally encountered in field use the filter pads can be relied upon to be about 90% efficient in removing parathion from the air.

Respirator filter pads made of alpha-cellulose were used to measure exposure to liquid sprays. For measuring exposure to dusts, pads were made by pressing 32 thicknesses of surgical gauze tightly together and cutting the gauze to the same size as a respirator pad. Then, this round piece of gauze was stapled to an alpha-cellulose respirator pad. When placing this pad unit in the respirator, the gauze side must face outwards, so that it will trap the dust particles. The main purpose of the alpha-cellulose pad is to hold the gauze in position. Care must be taken in removing the pads from the respirator after exposure, in order to prevent loss of dust.

Before either cellulose or gauze filter pads are used, they should be pre-extracted with the selected solvent to remove any soluble material that might interfere with the chemical analysis. To recover the toxicant after exposure, the entire filter pad is placed in a Soxhlet extractor for extraction in preparation for chemical analysis. The total amount of toxicant recovered from the pad (single-unit) or pads (double-unit respirator) is considered the amount to which the worker was exposed by the respiratory route during the exposure period. The amount of toxicant received per hour or per working-day by this route can then be calculated.

Alpha-cellulose respirator pads containing printing were found to be unsatisfactory even after extraction, because the ink interfered with chemical analysis. Certain respirators are provided with pads made of a fluffy material, possibly of synthetic composition. These pads also were found to interfere with the analysis of parathion, apparently because of their oil content. If plain unprinted respirator pads cannot be obtained, they can be cut from alpha-cellulose sheets.

When using the methods described above for calculating respiratory exposure, it should be kept in mind that the values obtained will relate to the amount of toxicant that is taken in through the nares and not necessarily the amount that actually enters the lungs.

DERMAL EXPOSURE

Direct methods for measuring the potential dermal exposure of workers have been developed. Although the methods of measurement appear to be quite accurate, there is probably a greater disparity between exposure and absorption for the dermal than for the respiratory or oral routes. Further, the degree of disparity must vary widely for different compounds.

Estimation of dermal exposure from air concentration

Edson (*op. cit.*) has provided a table for conversion of air concentration values to surface contamination rates at various wind velocities. The table is based on the assumption that the surface retains all spray particles approaching it at right angles. The table was used by Edson to show that, for various aerodynamic reasons, the surface contamination that he observed was, in the absence of splashing, much less than would be predicted on the basis of the assumption used. Even if more realistic assumptions were made, the prediction of dermal exposure from air concentration would be difficult because the many different surfaces and movements involved would create an extremely complicated aerodynamic situation.

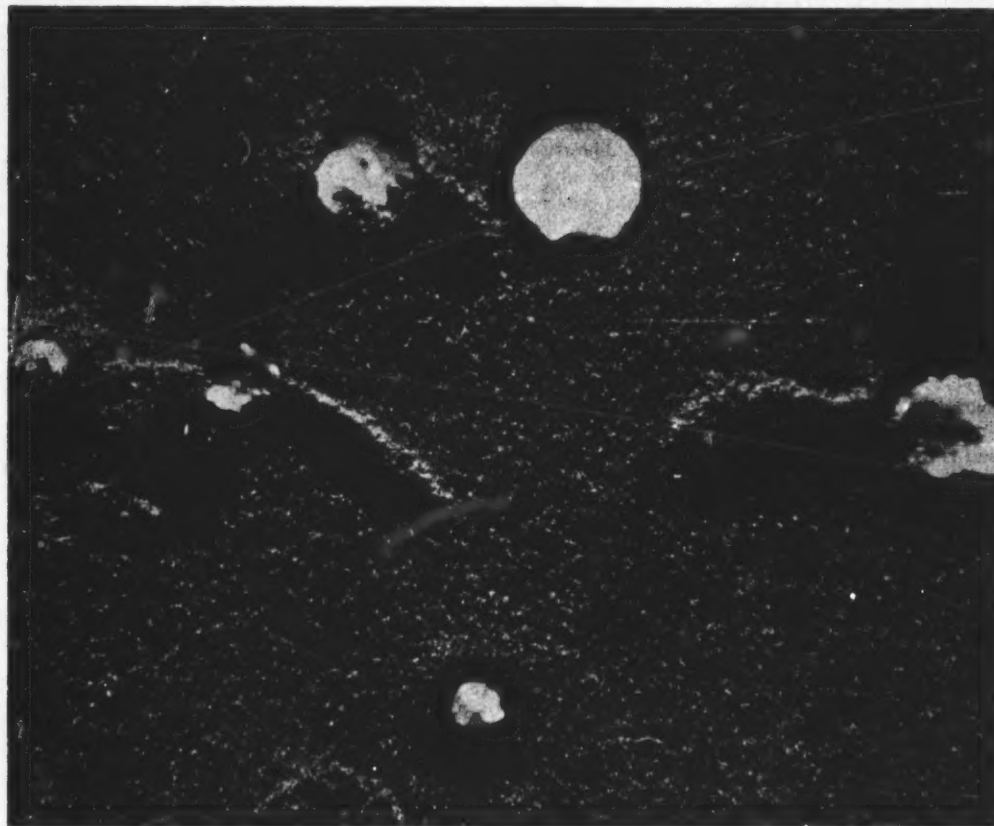
The physical behaviour of an aerosol is determined by the size of its particles. The size of the particles, in turn, is determined by the nozzle, the spraying pressure, and the characteristics of the material being applied. Within the range of emulsions and solutions used as insecticides, it is the nozzle and pressure that are important. However, in connexion with water-wettable powders, it is the fineness to which the powder itself is ground that limits the size of the smallest poison-bearing particles that reach the sprayman. Mere passage through the sprayer will not make the powder finer, though it may separate particles that would otherwise adhere. Microscopic study of water-wettable spray particles collected on carbon-coated slides attached to the brim of a sprayman's hat showed that:

(a) Some water-wettable powder particles are moist but not surrounded by water droplets at the time they reach the sprayman. This is shown by the relative size of the crater and by the manner in which the particles pick up carbon as they roll over the surface.

(b) The particles are usually single and not aggregated when they reach the sprayman.

FIG. 2

PATTERN MADE BY WATER-WETTABLE SPRAY PARTICLES ON CARBON-COVERED SLICE



Highly magnified.

(c) Apparently, some droplets of water that reach the sprayman do not carry particles of water-wettable powders, as indicated by empty craters on the carbon surface.

(d) The particles have only a small momentum, as judged by the feeble imprints they make on striking a soft film of carbon.

A typical microscopic field is shown in Fig. 2. The behaviour of the particles is of interest in considering the exposure of spraymen. Many of the insecticide-bearing particles are too large to inhale. It appears that many particles that reach dry skin may not adhere firmly enough to remain very long.

There is reason to believe that the amount of insecticide carried by a particle of water-wettable powder or a droplet of emulsion or solution is proportional to the size of the particle. It follows that there is a special interest in protecting workers from the larger particles, which carry the greatest amount of poison.

Direct measurement of dermal exposure using spray-absorbent or dust-retaining materials

One method for the direct measurement of dermal exposure involves placing absorbent pads at various points on the worker's body and allowing him to go

about his usual spray operations for a measured period of time, usually one or more complete spray cycles. Then, the pads are removed and carried to the laboratory, where the toxicant is extracted. Chemical analysis indicates the exposure of the various body parts sampled.

Pads made from alpha-cellulose have been used for the studies with sprays, while pads for dust have been made from surgical gauze. Pads of alpha-cellulose, 4 inches (10.2 cm) square, were cut from the large sheets obtained from the manufacturer. Gauze pads of the same size were prepared by stapling together 32 thicknesses of surgical gauze. The gauze pads were backed by a single sheet of white filter paper and bound with masking tape on all four edges. Gauze pads this size, after being bound with tape, measure approximately $4\frac{1}{2}$ inches (11.4 cm) on each edge, and are bound so that an area of gauze approximately $2\frac{1}{2}$ inches (6.4 cm) on each edge is left exposed on one side.

The alpha-cellulose pads are absorptive and yet do not generally become soaked with spray during exposure. Similarly, the operator's skin does not ordinarily get wet to the point of run-off; so it is assumed in this connexion that both pads and skin retain all the spray that impinges on them.

Fletcher et al. (1959) explored the use of pads impregnated with lanolin in studying the dieldrin exposure of spraymen. They pointed out that it was possible to argue that non-greasy pads placed next to the skin do not simulate the slightly greasy surface of the skin, and hence the average pick-up recorded would be too low. Their lanolin-impregnated pads did not prove satisfactory, however. The lanolin interfered with the chemical determination, resulting in a very high blank value. The skin absorbed lanolin from the pads in varying degrees depending on the amount of sweating that occurred where the pads were attached, causing the blank value to vary from one part of the body to another. Fletcher and his co-workers thus concluded that for use in measuring exposure plain pads were preferable to lanolin-impregnated ones.

Laboratory tests with known quantities of dust indicated that surgical gauze pads prepared as noted above retained approximately 90% of the dust applied to them even though they were held in an inverted position and shaken in a mechanical shaker after exposure. It is nevertheless advisable to handle the dust pads carefully after exposure so that trapped dust particles will not be lost. Furthermore, pads are not effective in some situations; for example, not

only the dust but the pads themselves may be lost if they are attached to pilots in small, open aircraft.

Before being made into pads or bag liners, all alpha-cellulose, surgical gauze, and filter paper should be pre-extracted using the same solvent to be used later at the analysis stage. However, as indicated above for respirator pads, such extraction is not always adequate to remove inks and oils; so pads bearing these materials should not be used.

The pads are attached to various parts of the operator's body or clothing by means of two strips of pressure-sensitive masking tape one inch (2.5 cm) wide. About one-half of the width of the tape covers the edges of the pad and the other portion of the tape sticks to the clothing or skin. Considerable variation was noted in the adhesive quality of various brands of tape. Some were not sufficiently adhesive to stick to waterproof rubberized clothing while others were so sticky that it was painful to remove them from the skin. Some, however, proved satisfactory.

Exposure pads can be used over or under clothing and on almost any portion of the body. The routine test, however, involves a total of ten pads. The pads are attached in the following locations: at the front of the legs just below the knees, front of the thighs, back of the forearms, top of the shoulders, back of the neck (upper edge of the collar), and upper chest on or near the jugular notch. The latter two are placed as close to the exposed neck as possible.

Dermal exposure in the mouth-nose area can be checked, using a pad held in place by rubber bands, stretching from binder clips on each side of the pad to the ears. Also, strips or bands of alpha-cellulose can be fastened around the head, forearm, leg, or other body part in order to determine more completely the over-all exposure of irregular areas. This device can be used around the leg just above the shoe to determine if spray material drifts up under the trouser.

If the subject's clothing appears to be excessively contaminated, it is advisable to staple a piece of glazed powder paper to the back of the pad to prevent contamination from the clothing. The paper is removed before extraction.

At the completion of an exposure period, the pads are removed from the worker, the tape pulled from the edges of the pads, and each pad placed in a waxed-paper sandwich bag between the folds of a piece of qualitative white filter paper. Then the sandwich bag is labelled with a glass-marking pencil, the top is folded over and stapled closed, and the bag

is placed in a container for transport to the laboratory.

This procedure cannot be done very quickly. When working in the field with operators of spray or dust machines, it is important that their work should not be slowed too much if one wishes to maintain continued co-operation. Therefore, in practice, the pads are removed from the operator as quickly as possible; and, as each pad is removed, it is placed in a compartmented box. A corrugated paper carton made for 12 one-pint (about 0.5-l) wide-mouthed glass canning jars is satisfactory. The individual compartments are spaced approximately $3\frac{3}{4}$ inches (9.5 cm) apart, allowing room for the pad to be placed on edge diagonally across the compartment space so as to prevent cross-contamination between the box and that portion of the pad to be analysed. The compartments are labelled for the portions of the body to which the pads are attached. After the sprayman has returned to his work, the pads can be inserted in the bags and labelled.

In making measurements of exposure to operators of spray or dust machines, care is used to ensure that each exposure period includes one complete cycle or more of spray or dust application. Each cycle ordinarily includes the following operations: loading the toxicant into the dispersing machine, proceeding to the spraying or dusting site, application of the material, and returning to the loading site. The exposure period is timed so that the amount of exposure the operator is subjected to in an hour or a working-day can be calculated.

In the laboratory, the double layer of filter paper and the exposed pad are removed from the bag and a square area 2 inches (5.1 cm) on the edge is cut from the centre using a paper trimmer. This practice removes areas around the edge of the pad where there may be bits of tape or contamination from handling. In the case of dust exposure pads, this procedure removes the border tape that holds the gauze and backing together. Then, the 4-square-inch (25.8-cm²) section of pad and filter paper is placed in a Soxhlet apparatus for extraction. The total amount of toxicant determined in the extract is a measure of the exposure on the 4-square-inch test area of the body part involved.

The amount of pesticide that comes into contact with unprotected skin areas of spray operators can then be calculated. Usually, it is assumed that the average minimum clothing worn includes shoes, socks, long trousers, a short-sleeved open-necked shirt, and no hat, no respirator, and no gloves. It

is, of course, realized that this is an empirical estimate and that some spraymen wear more and some wear less protection. Many spraymen wear a hat, gloves, and a light protective jacket. Less commonly, workers wear a respirator. The surface areas of the usually unclothed body parts are determined using Berkow's method (Berkow, 1931). The areas of the body parts most commonly involved are: face, 0.70 square feet (0.065 m²); hands, 0.88 square feet (0.082 m²); forearms, 1.30 square feet (0.121 m²); back of neck, 0.12 square feet (0.011 m²); and front of neck and "V" of chest, 0.16 square feet (0.015 m²).

The total exposure is the sum of the dermal exposure of the usually unclothed body parts and the respiratory exposure. The total calculated exposure expressed as mg per kg can be compared with dosage levels that produce different degrees of injury in experimental animals. However, precise animal data are often lacking for respiratory toxicity. In this event, a weighting factor should be used to take into account the more rapid and more complete absorption of respiratory as compared with dermal doses of toxicant. A factor of 10 has been adopted empirically for this purpose.

Calculations are usually made on the basis of an eight-hour working-day.

One shortcoming of the pad technique is the necessary assumption that the pad area is representative of the entire body part being measured. A procedure which has been found useful, particularly for uneven body surfaces, involves the use of knit white cotton garments that cover the study area during exposure. Gloves have been used for measuring exposure of the hands, T-shirts (short-sleeved undershirts) for upper body exposure (particularly for estimating the amount of toxicant that penetrates outer clothing), socks for foot exposure (particularly for determining the amount of pesticide that penetrates the shoes when one walks in wet cover crops in recently sprayed areas), and socks with the feet cut off for measuring exposure around the forearms, lower legs, and ankles. Occasionally, a garment may have to be cut off the subject to avoid contamination by some part of the body over which it would normally be slipped in the process of removal. This is nearly always the case with the T-shirt. The upper portion of a sock being used as a measuring device on the arm can be installed or removed over the normally contaminated hand by first placing a plastic bag over the hand and slipping the sleeve over it. Uncut or resewn garments can be laundered and re-used after extraction of toxicant.

Direct measurement of dermal exposure using swabs and liquid rinses

Another method of measuring skin contamination with toxic sprays or dusts involves swabbing or rinsing the skin with a solvent that will remove the toxicant and then analysing the rinse solution. As pointed out in detail below, this method appears to give a somewhat more accurate measure of dermal exposure than the procedures described above, especially where hands and other irregular areas are involved.

For the swabbing technique, two eight-ply 4×4-inch (10.2×10.2 cm) pre-extracted surgical gauze sponges are placed together and folded twice to form a 2×2-inch (5.1×5.1 cm) square, which is stapled near the folded edge. The swabs that are to be used in swabbing a given area are placed in a jar and saturated with 95% ethyl alcohol. The jar is sealed ready for use in the field. The inside of the jar lid is covered with aluminium foil to prevent erosion of the original liner. Each swab is grasped at the stapled edge with forceps, the excess alcohol is squeezed off against the inside of the jar, and the area of skin to be checked is swabbed, using the forceps as a handle to rub the cloth with light pressure back and forth over the area. After the last swab has been placed back in the jar, the jar is labelled and returned to the laboratory for analysis.

A single washing with such a swab was found to be insufficient to remove all the toxicant, particularly under field conditions of fairly heavy exposure. In an experiment involving 21 sets of swabbings for removal of parathion from the back of the arms and hands of spraymen, it was determined that the use of four swabs on an area the size of the back of the hand, or the back of one-half the length of the forearm, at the rate of 25 strokes with each swab removed an average of 91% of the total amount of parathion recovered with the six separate swabs used in the test. The amount of parathion found on the fifth swab was near or below the lower limit of the sensitivity of the test in most cases. Therefore, four swabs were considered adequate to remove 90% of the toxicant. An obvious precaution is that the skin to be tested must be cleaned before the exposure period begins. This is done by swabbing the test area before exposure in the same manner as that used after exposure.

Use of the swab method for estimating contamination of the hands is not entirely satisfactory. It is not easy to swab correctly between the fingers and around the fingernails. With the number of swabs

that must be used to ensure adequate recovery of the toxicant, the procedure is time-consuming and therefore unpopular with the working subjects.

The solution to these problems appears to be the use of polyethylene bags containing a suitable solvent for washing the toxicant from the hands. The hand to be checked is inserted into a bag containing a given amount of solvent; and, while the open end of the bag is held tightly around the arm or wrist to prevent leakage, the thumb and fingers are rubbed against one another and against the palm. Then the hand and bag are shaken vigorously about fifty times. For measuring parathion exposure by this technique, 95% ethyl alcohol has been found to be a satisfactory solvent. The person whose hand is being checked is asked to cup his hand slightly and hold his fingers a short distance apart during most of the shaking operation. This allows thorough rinsing around the fingers. Occasionally, the thumb and fingers should be rubbed against one another and against the palm to help loosen adhering material and thus increase efficiency of the washing process. The usual area checked is from just above the wrist to the tips of the fingers. This is the area usually exposed when long sleeves are worn. Bags that are most suitable for this purpose are made of polyethylene tubing (thickness of material 0.0015 P.E.) 7 inches (17.8 cm) wide. The tubing is cut off in 16-inch (40.6 cm) lengths, and one end of each piece is sealed with a heat-seal roller, to form a bag.

Bags made with seams down the sides have not been satisfactory because the large amount of heat-sealed seam allows a greater chance of weak spots, resulting in leaks. The bags can be re-used if they are turned inside out and rinsed thoroughly with alcohol; however, the cost of alcohol and the time involved in cleaning more than offset the cost of bags so that re-use is not economical.

The rinse unit is prepared for field use by first pouring 200 ml of 95% ethyl alcohol into a bag and then twisting the upper part of the bag to make an airtight seal. The twisted portion is held tight with a clip. The bag is then placed in a pint (about 0.5 l) wide-mouthed canning jar and the lid screwed tightly in place. The jar lid unit (made up of a lid and retaining ring) is held together by placing a 2-inch (5.1 cm) piece of masking tape across the ring and lid when they are in place on the jar. This one-piece top facilitates installation and removal of the bag. The tape is also used as a place to label the sample. After the rinse operation, the bag top is again twisted closed, the clip fastened in place, and

TABLE 2
REMOVAL OF PARATHION FROM HANDS BY MEANS OF
BAG RINSE

Amount of exposure	No. of tests	Value	Percentage of extractable parathion ^a removed by	
			1 rinse	2 rinses
Light	10	Range	77 to 90	89 to 96
		Mean $\pm$ SE ^b	81.9 $\pm$ 0.8	92.7 $\pm$ 0.7
Medium	18	Range	81 to 94	94 to 98
		Mean $\pm$ SE	89.6 $\pm$ 0.6	96.9 $\pm$ 0.2
Heavy	8	Range	79 to 94	95 to 98
		Mean $\pm$ SE	88.1 $\pm$ 2.0	96.6 $\pm$ 0.4
Total or mean	36	Range	77 to 94	89 to 98
		Mean $\pm$ SE	84.4 $\pm$ 0.9	95.6 $\pm$ 0.4

^a The amount removed by 3 rinses is considered to represent 100%.

^b Standard error of the mean.

the bag placed back in the jar ready for transport to the laboratory for analysis.

As with the swabbing technique, a single bag rinse was found to be insufficient to remove all the recoverable toxicant. An experiment involving 36 sets of bag rinses was conducted to determine how many rinsings were necessary to remove the parathion from the hands of spray operators immediately following a period of spraying in orchards. Preliminary tests had shown that the amount of parathion recovered in the third rinse was usually less than 5% of the total recovered, and each succeeding rinse recovered progressively smaller amounts. In Table 2 is shown the percentage of toxicant removed by one and by two rinses immediately following exposure. In this table, the amount of parathion removed by three rinses is considered to represent 100%. One rinse removed from 77% to 94% with a mean of 84.4% of the total and two rinses removed from 89% to 98% with a mean of 95.6%. Rinsing appeared to be slightly less efficient after light exposure than following medium or heavy exposure. On the basis of these results, use of two bag rinses for each hand appears to be a satisfactory procedure.

Adsorption or binding of the toxicant by the skin apparently has an effect on recovery of parathion by the rinsing procedure. In tests carried out 12 hours or more after termination of exposure, lower per-

centages of total recoverable parathion were removed with each rinse in comparison with tests carried out immediately after exposure. Preliminary investigations into the removal of parathion one to several days following exposure indicated that four bag rinses may then be necessary for removal of 90% of the recoverable toxicant.

Studies have been carried out to determine the relative efficacy of rinsing as compared with swabbing as a measure of hand contamination with DDT and with parathion. For a given individual following a period of exposure, one hand was rinsed with ethyl alcohol and the other swabbed with the same solvent. The treatments were alternated between right and left hands. In 15 comparisons using DDT, the bag rinse technique removed an average of 1.7 times as much of the toxicant as did swabbing. In 18 comparisons using parathion, an average of 2.4 times as much contamination was removed by the bag rinse as by swabbing. These results are summarized in Table 3.

Similar comparisons also have been made on the dorsal surface of the forearm between the effectiveness of the alpha-cellulose pads and that of swabbing. No significant difference between these techniques was noted with either DDT or parathion.

ORAL EXPOSURE

If the hands are contaminated or if contaminated objects are placed in the mouth, oral exposure to a pesticide may occur during eating, drinking or smoking. Oral exposure may result also from swallowing inhaled material that impinges on the mucous membranes of the upper respiratory tract. The

TABLE 3
EFFECTIVENESS OF VARIOUS TECHNIQUES IN
MEASURING DERMAL EXPOSURE TO DDT AND
PARATHION

Compound	No. of samples	Recovery (μ g)		
		Pad	Swab	Bag rinse
DDT	15	—	27.6 $\pm$ 2.5 ^a	47.6 $\pm$ 3.0
	9	761 $\pm$ 77	632 $\pm$ 44	—
Parathion	18	15.9 $\pm$ 2.3	17.3 $\pm$ 2.6	—
	18	—	707 $\pm$ 128	1 715 $\pm$ 344

^a Standard error of the mean.

blowing out of clogged spray nozzles or some other violation of proper procedure may produce direct oral exposure. There seems to be no proven, adequate, experimental technique available for estimating oral exposure. The analysis of vomitus or of stomach washings is informative and lavage may be done experimentally as well as therapeutically.

Indirect measurement of oral exposure by tagging the pesticide to be studied with a water-soluble dye such as methylene blue has been considered. Since dermal absorption of methylene blue is minimal, urinary excretion of the dye would then be a measure of oral contamination by the formulation being used. This proposal has not, to the authors' knowledge, been tested experimentally.

RESULTS BY DIRECT METHODS

The methods described above or slight modifications of them have been used in a number of studies to measure the exposure of workers to various pesticidal compounds during different conditions of actual use.

Batchelor & Walker (1954) found that the average concentration of parathion in air during orchard spraying was less than 0.1 mg per m³ (the industrial threshold limit), except for samples taken during mixing or loading operations. Average values ranged from 0.03 to 0.09 mg per m³ depending on the formulation and method of application used. Assuming a tidal air volume of 480 litres per hour, it was calculated that the inhalation of parathion during high-pressure hand spraying was 0.04 mg per hour and during air-blast spraying was 0.06 mg per hour. The respiratory exposure to parathion for a 70-kg man working an eight-hour day was estimated to be 0.005 and 0.007 mg/kg for high-pressure hand and air-blast spraying, respectively.

The values for concentration of parathion in air reported by Batchelor & Walker agreed quite well with the figures obtained by the American Cyanamid Company (1951) in California citrus groves and by Stearns and his co-workers (1951) in a Florida citrus grove, but were lower than the concentrations found in Quebec apple orchards by Kay and associates (1952). Braid et al. (1955), studying the parathion content of air samples taken at various distances from a parathion duster, found concentrations exceeding 0.1 mg per m³ up to about 260 feet (or about 80 m) away. None of the latter four groups used their air concentration figures to calculate respiratory exposure values.

In studies during ground application of insecticides to forests, Wassermann et al. (1960) found air concentrations varying between 2.6 and 12.5 mg per m³ for γ -BHC and 4.6 and 25.5 mg per m³ for DDT. On the basis of these values the workers had a calculated respiratory exposure in an eight-hour working-day of 0.35-0.93 mg/kg for γ -BHC and 0.56-2.43 mg/kg for DDT. In an airplane spraying programme, air concentrations breathed by workers varied from 4.1 to 53.7 mg per m³ for γ -BHC and from 18.9 to 170.9 mg per m³ for DDT. These levels determined respiratory exposure values of 4.2-5.6 mg/kg/8 hours for γ -BHC and 15.0-20.9 mg/kg/8 hours for DDT.

During airplane application of malathion for mosquito control, Caplan and his associates (1956) found average air concentrations of 0.067 and 0.088 mg per m³ in unprotected and in semi-sheltered areas, respectively. One hour after spraying, corresponding values were 0.044 and 0.034 mg per m³, respectively. One sample taken inside a building contained 0.014 mg per m³. Respiratory exposure during spraying was calculated to be 55 μ g/hour outdoors and 12 μ g/hour indoors.

Batchelor & Walker also estimated respiratory exposure using the respirator pad technique. By this method, they found an inhalation of 0.19 mg of parathion per hour or 0.022 mg/kg per day in high-pressure hand spraying and 0.16 mg per hour or 0.018 mg/kg per day with air-blast equipment. Comparison of values derived by the two methods indicated that the respirator pad technique gave values that were 3 to 5 times as great as those determined on the basis of air concentration values. It should be noted that these workers did not shield their respirator pads to prevent impingement. Correcting Batchelor & Walker's respirator pad figures on the basis of the above-demonstrated ratio of impinged to inhaled toxicant (i.e., 3 to 1), one derives respiratory exposure values of the same order of magnitude determined from their air concentration studies.

Wolfe and his co-workers (1959) in evaluating health hazards involved in indoor house spraying with DDT determined respiratory exposure by both air concentration and respirator pad methods. They found an average air concentration of 7.1 mg of DDT per m³, which exceeded the recommended industrial threshold limit of 1 mg per m³. The calculated inhalation of DDT based on these air concentration values was 3.4 mg per hour (or 0.39 mg/kg per day). The respiratory DDT exposure calculated from funnel-covered respirator pad values was 7.1

mg per hour (or 0.81 mg/kg/day). The values determined by these workers by the two methods were considered to be of about the same order of magnitude, although here also, as was noted above, the respiratory pad method gave a value about twice as high as the air concentration procedure. Using the respirator pad technique only, Wolfe et al. estimated that respiratory exposure of workers during outdoor house spraying for vector control was only 0.11 mg per hour.

Culver et al. (1956) measured the exposure of workers and of observers to malathion and chlordane during their use as aerosols for mosquito control. During a two-week period, five individuals were exposed to malathion for a total of 3.91-5.23 hours and to chlordane for 2.12-4.31 hours. Based on air concentration values, total respiratory exposure to malathion was 9-21 mg for the operators and 1-5 mg for the observers. Exposure to chlordane was 3-5 mg for the operators and 2-4 mg for the observers. The respirator pad technique gave values for malathion exposure of 0.1-1.2 mg and 0.2-0.4 mg for workers and observers, respectively. The values for chlordane for these groups were 0.2-1.3 mg and 0.2-0.4 mg.

Thus, in contrast to the results of Batchelor & Walker and of Wolfe et al., Culver and his associates found that air concentration values gave higher figures for respiratory exposure than did respirator pads. However, Culver et al. pointed out that, in some instances in their study, respirator pads were not worn for the entire exposure period. They used an average breathing rate of 14 litres per minute (840 litres per hour) in their calculations, while the previously mentioned work was based on 480 litres per hour. The difference in these two factors would not seem to be great enough to account for the differences in results, however. Other factors that may also have contributed include the fact that different compounds, different formulations, and different methods of application were used. For collecting air samples, Culver et al. used the midjet impinger rather than the Greenburg-Smith impinger employed by Batchelor & Walker and by Wolfe et al.

Using respirator pads only, Batchelor et al. (1956) estimated that orchard workers using dinitro-ortho-cresol (DNOC) for blossom thinning on fruit trees inhaled about 0.4 mg per hour. Quinby et al. (1958), using the same technique, failed to detect methyl parathion and Guthion in the air breathed by cotton checkers; the method was capable of measuring 10-20 µg of methyl parathion per hour and 20-40 µg of

Guthion per hour depending on the size of the sample. Also, using the respirator pad technique only, it has been estimated that workers using dinitro-ortho-secondary-butylphenol (DNOSBP) for weed control inhaled 0.12 mg per hour.¹

Studies of dermal exposure using some of the techniques described above have been reported by several authors.

Batchelor & Walker (1954) estimated that an orchard sprayman wearing a short-sleeved, open-necked shirt and no hat or gloves would receive a dermal contamination of 55.8 mg of parathion per hour while using a high-pressure hand sprayer and 77.7 mg per hour during air-blast spraying. Batchelor et al. (1956) calculated that workers exposed to DNOC during blossom thinning would receive a dermal contamination of 63.2 mg per hour. Wolfe et al. (1959) reported a dermal exposure of 1755 mg per hour during indoor spraying with DDT and 243 mg per hour during outdoor house spraying. Hughes & Read (1959) determined the dermal exposure of greenhouse workers to parathion-treated tomato and cucumber plants by analysing gloves worn by the workers. These authors estimated an exposure of the order of 10 mg or 0.14 mg/kg for an eight-hour working-day.

During outdoor aerosol application, Culver et al. (1956) found dermal malathion contamination of 12-387 mg for workers and 11-27 mg for observers; chlordane exposures were 4-31 mg for operators and 3-7 mg for observers during the entire period of observation. Quinby et al. (1958) observed that the dermal exposure of cotton checkers to methyl parathion was 0.7-3.2 mg per hour and to Guthion, 5.3-18.4 mg per hour, depending upon the age of the residue. Caplan et al. (1956) found dermal exposure during airplane application of malathion for adult mosquito control to average 0.89 mg/hour outdoors and 0.24 mg/hour indoors during a two-hour spray period and two hours thereafter.

A dermal exposure of 124.1 mg per hour has been reported for workers using DNOSBP for weed control.¹

Using an exposure pad technique similar to that described above, Fletcher et al. (1959) determined the dermal exposure of spraymen using dieldrin in residual spraying to be 1.8 mg/kg per day. In estimating dermal exposure, these authors used total body surface area (average, 1.73 m²) and the average

¹ Wolfe, H. R., Durham, W. F. & Batchelor, G. S. Manuscript in preparation.

TABLE 4
EXPOSURE OF WORKERS TO PESTICIDES WHILE
CARRYING OUT VARIOUS ACTIVITIES

Compound	Activity	Exposure		
		Dermal (mg/man/ hr)	Respira- tory (mg/man/ hr)	Total (percent- age of toxic dose per hour ^a)
Parathion	Spraying apples	77.7	0.2	5.4
Chlorthion	Applying aerosol	3.0	0.3	0.003
Malathion	Applying aerosol	6.6	0.3	0.003
Guthion	Checking cotton	5.4	^b	0.004
Methyl Parathion	Checking cotton	0.7	^b	0.002
DDT	Spraying apples	274	0.12	0.15
DDT	Indoor house spraying	1 755	7.1	1.02
DDT	Spraying house outside	243	0.11	0.14
DNOC	Spray-thinning apples	63.2	0.4	0.25
DNOSBP	Applying as herbicide	88.7	0.12	0.57

^a Calculated for 70-kg man on the basis of dermal LD₅₀ to male white rats or guinea-pigs.

^b Value obtained was below experimental limits of chemical method.

amount of dieldrin (65 mg/m²) recovered from pads placed directly on the skin of various clothed and unclothed parts of the bodies of men who averaged 62 kg in weight.

Wassermann et al. (1960) found that the dermal exposure of ground operators during eight hours applying insecticides to forests was 8.0 mg/kg for γ -BHC and 24.3 mg/kg for DDT.

In Table 4 are summarized the dermal and respiratory (based on respirator pad) exposures for workers exposed to various compounds during different activities. It is of interest to note here the fact that, in these situations, the respiratory exposure represents only a small fraction of the dermal

exposure. This fact has been recognized by several authors (Batchelor & Walker, 1954; Batchelor et al., 1956; Wolfe et al., 1959). The data obtained by these authors indicate that, even considering the more rapid and more complete absorption of toxicant drawn into the lungs as compared with that deposited on the skin, dermal exposure appears to be more important on the basis of the fractional part of the toxic dose potentially absorbed than is respiratory exposure. It should be noted that the studies cited in Table 4 were all carried out with liquid sprays. The relationship between dermal and respiratory exposure may be different for dust formulations. In connexion with the disparity pointed out above in the respiratory exposure results with chlorthion and malathion, it should be pointed out here that the respiratory exposure values for these two compounds represent a much greater fraction (4.5%-10%) of the dermal exposure value than for any other compound studied (1% or less).

Also shown in Table 4 are exposure values calculated on the basis of the fraction of the toxic dose absorbed per hour. The toxicity figures were extrapolated on the basis of studies with laboratory animals. The formula used for the calculation was:

Percentage of toxic dose =

$$\frac{\text{Dermal exp. (mg/hr)} + [\text{Resp. exp. (mg/hr)} \times 10]}{\text{Dermal LD}_{50} \text{ (mg/kg)} \times 70} \times 100$$

Study of the table indicates that for any given insecticide there appears to be a significant variation in hazard depending upon the type of activity in which one is engaged. For example, indoor house spraying with DDT seems to be about 7 times as hazardous as spraying apples or as outdoor house spraying with the same compound. Further, the lower concentrations used in application of more toxic materials may not be enough to compensate for their inherently greater toxicity. The difference is even greater when contamination by concentrates during mixing is taken into account. The largest fractional toxic dose on the table is represented by the 5.4% per hour applicable to spraying apples with parathion.

INDIRECT METHODS

Any measure of absorption or its necessary sequelae constitutes an indirect measure of exposure. It is not often convenient to measure absorption

itself, but measurement of a compound or its biotransformation products in the blood, tissues, or excreta gives information on minimal absorption.

Exposure to DDT can be estimated on the basis of DDT storage in fat (Mattson et al., 1953) or DDA excretion in urine (Cueto et al., 1956). The former procedure has been used quite widely. The most extensive study is that of Hayes et al. (1958). DDA excretion of volunteers ingesting daily doses of DDT has been reported by Hayes et al. (1956), and DDA excretion of workers occupationally exposed to DDT has been determined by Ortelée (1958). Urinary *p*-nitrophenol excretion can be determined (Elliott et al., 1960) and used as a measure of exposure to parathion or other compounds yielding *p*-nitrophenol or one of its congeners on hydrolysis (Arterberry et al., 1961).

Somewhat different information on absorption is given by measurement of a physiological change produced by the compound—for example, the inactivation of cholinesterase by organic phosphorus compounds. The electrometric procedure of Michel

(1949) together with a micro modification of this technique for use with capillary blood samples (Marchand, 1952) is probably the most widely used method. There are also available colorimetric (Metcalf, 1952), titrimetric (Brown & Bush, 1950), and manometric (Ammon, 1933) procedures. Surveys of exposure of workers and others to organic phosphorus insecticides using the blood cholinesterase level as the criterion have been reported by Ingram (1951), Kay et al. (1952), Sumerford et al. (1953), Bruaux (1957), Hayes et al. (1957), Petty et al. (1959), Bruaux (1960), and Lebrun & Cerf (1960).

It has been shown by Arterberry et al. (1961) that urinary excretion of *p*-nitrophenol is a more sensitive measure of exposure to parathion than is the blood cholinesterase level in that people with very slight exposure may show excretion but show no change of blood cholinesterase.

DISCUSSION

There are advantages and disadvantages involved in both direct and indirect methods of measuring exposure. Direct measurement of a pesticide in samples collected during spraying is frequently easier than measurement of the same compound or its derivatives in tissues and other biological materials. Although the direct method gives an estimate of total potential exposure, it does not give information on the portion of contacted material that is actually absorbed.

Any attempt to relate directly or indirectly measured exposure to clinical effect must take into account the following facts. (1) A poison must be absorbed in order to cause harm. (2) The significance of absorption by various routes may differ greatly according to the rate of local detoxification of the compound associated with those routes. (3) The degree of storage depends chiefly on the compound, the species, the dosage, the duration of dosage, and the route of administration. Not only are the magnitude of each dose and the number of daily doses important for clinical effect, but also the distribution of the dose within the day may be critical. (4) Injury may or may not be a direct function of the concentration of poison present at the moment in some critical tissue.

Results of the direct measurement of exposure to pesticides may be used in evaluating the relative hazard of different routes of exposure, different

operational procedures, and different protective devices. Results of the indirect measurement of exposure may be of use for the same purposes; in addition, these "indirect" measures are more useful in relating exposure under observed conditions to clinical effects.

There is not a single pesticide for which the interrelationships between occupational exposure to different formulations by different routes, the fate of the compound in the body, and its clinical effects are all adequately known.

With most of the compounds and activities studied (Table 4), it is not surprising that cases of poisoning associated with occupational exposure have not been seen. The fractional toxic doses represented by one hour of ordinary exposure are simply so low and involve such large safety factors (as measured by the fractional toxic dose) that working unusually long hours or some carelessness or accidents or a combination of these factors are not sufficient to raise the exposure to the danger level.

This reasoning does not, however, hold true for parathion. Numerous illnesses and an occasional death occur each season in persons occupationally exposed to parathion. When one considers that a sprayman is potentially exposed to 5.4% of a toxic dose in one hour of spraying or 43% in an eight-hour day, these cases of poisoning are not surprising. In fact, on the basis of these figures, it would be easily possible for a

sprayman to expose himself to a toxic dose in the course of two days of work without any accidental, gross exposure. This would require only that he work 18.5 hours during the two-day period. Many orchardists work this long or longer during their busy spray season. The question that must then be answered is not "Why do some workers get poisoned by parathion?" but rather "Why do so few workers get poisoned by parathion?". The cause of the discrepancy is not understood fully.

Two observations that will be published in detail elsewhere¹ tend to confirm that, even with parathion, dermal absorption is slow and incomplete. These observations are as follows. (1) When measured quantities of parathion were placed on the skin of human volunteers, large fractions (up to 90%) could be recovered by washing the treated skin with alcohol as long as eight hours afterwards. (2) Significant quantities of parathion have been recovered from the hand of a sprayman as long as two days after his last exposure.

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RÉSUMÉ

L'emploi des pesticides dans la lutte contre les insectes vecteurs et ravageurs ne va pas sans risques. Chaque année on dénombre des décès et l'on signale de nombreux cas d'intoxication. Les empoisonnements professionnels causés par quelques-uns des plus récents composés organophosphorés, tout particulièrement le parathion, et certains des hydrocarbures chlorés, tels que la dieldrine, sont en général la conséquence de l'utilisation défectueuse du matériel ou de la négligence des travailleurs, qui ne revêtent pas les habits protecteurs convenables.

Il n'existe aucun pesticide pour lequel les rapports entre l'exposition professionnelle — quelle que soit la voie de pénétration —, l'évolution du produit dans l'organisme et les conséquences cliniques qui en résultent soient tous convenablement connus.

Les auteurs décrivent les diverses méthodes d'évaluation directe et indirecte des risques d'intoxication. Les premières ont pour objet le dosage des quantités de substances qui pénètrent dans l'organisme par voie respiratoire ou cutanée, les secondes évaluent les conséquences physiologiques de l'absorption des pesticides, telle que la modification des cholinestérases sanguines.

C'est habituellement en dosant la concentration dans l'air qu'on a évalué l'exposition à une substance toxique par la voie respiratoire. On peut aussi, lorsqu'il s'agit

d'aérosols solides ou liquides, déterminer la quantité de produit toxique recueillie sur la partie extérieure absorbante ou filtrante d'un masque à travers lequel respire le sujet pendant un certain temps, exactement connu. L'estimation, faite en circuit fermé au laboratoire, a montré qu'une moyenne de 90% du parathion, provenant d'aérosols de différentes formules était retenue par ce procédé.

Pour apprécier le dépôt cutané, on a utilisé des tampons absorbants, des gants de coton tricotés et d'autres vêtements portés par le travailleur, afin de collecter le pesticide pendant l'exposition. S'il s'agit de recueillir des produits vaporisés, on se sert de coussinets d'alpha-cellulose, mais, dans le cas de poussières, on préfère ceux qui sont faits de gaze chirurgicale. On peut également utiliser la peau elle-même comme surface collectrice: après un temps connu de travail, on enlève par lavage ce qui s'y est déposé. Le « lavage » doit consister en un nettoyage répété lorsque la plus grande partie de la surface corporelle est intéressée. Cependant, on mesure avec plus de précision et de facilité l'exposition cutanée des mains par rinçage avec un solvant convenable en utilisant un sac de polyéthylène comme récipient pour le liquide de lavage.

¹ Durham, W. F., Wolfe, H. R., Arterberry, J. D. & Elliott, J. W. Manuscript in preparation.

Aussitôt après le travail, 90%, ou même plus, du dépôt enlevable par ces méthodes peut être recueilli au moyen de quatre tampons distincts ou de deux sacs de rinçage. Lorsque les dépôts sont plus anciens, il faut un plus grand nombre de tampons ou de sacs.

On ne dispose pas encore de méthodes sûres pour doser l'absorption orale. Il est intéressant de noter que les plus grosses particules aspirées sont finalement avalées.

Parmi trois tests comparatifs, deux ont montré que la méthode du tampon donnait des résultats significativement plus élevés, pour l'étude de l'absorption par la voie respiratoire, que la technique de la concentration de l'air. Dans tous les exemples cités, l'importance de l'exposition cutanée était beaucoup plus grande que celle de l'exposition respiratoire, même si l'on tient compte du fait que les produits toxiques inhalés sont absorbés plus rapidement et plus complètement qu'ils ne le sont par voie dermique.

L'appréciation des complications consécutives à l'absorption permet une estimation indirecte des risques. Il est souvent difficile de préciser l'absorption elle-même, mais le dosage d'un composé, ou de ce qui résulte de ses modifications par suite de l'activité biologique, dans le sang, les tissus, ou les excréta, peut donner un chiffre d'absorption minimum. On obtient des renseignements quelque peu différents en étudiant les effets physiologiques causés par le produit considéré, par exemple l'inactivation de la cholinestérase par les composés organophosphorés.

Pour tout essai de relier directement ou indirectement les conditions connues d'exposition et les manifestations cliniques, il faut tenir compte du fait que l'absorption peut présenter de grandes différences selon l'importance de la désintoxication locale, en relation avec la voie de pénétration suivie; que l'accumulation du produit dépend principalement de ses propriétés, de la quantité absorbée et de la voie d'absorption (l'importance de chaque dose et le nombre de doses quotidiennes ne sont pas seuls en cause, la répartition dans la journée peut avoir son influence); que les dommages peuvent être, ou ne pas être, en relation directe avec la concentration du produit toxique présent au moment considéré dans un tissu critiquelement sensible.

Le dosage d'un pesticide dans des échantillons collectés fréquemment pendant des vaporisations est plus facile que celui du même produit ou de ses dérivés dans les tissus ou dans d'autres produits biologiques. Ces considérations et les effets physiologiques qui ont été mentionnés précisent quelques-unes des possibilités et des limites de la méthode de dosage direct de l'absorption.

Les résultats des dosages directs de l'exposition aux pesticides peuvent être utilisés pour comparer les risques encourus suivant les voies diverses d'exposition, pour apprécier les différentes techniques d'emploi des composés chimiques et les divers moyens de protection. Les résultats des dosages indirects de l'exposition peuvent en outre être plus utiles dans certaines conditions pour établir le rapport entre l'exposition et les conséquences cliniques.

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*Clinical Aviation and Aerospace Medicine***Chronicle of a Cropduster Crash: A Devastating and Avoidable Tragedy**

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WATSON, M., and W. W. BENSON. *Chronicle of a cropduster crash: a devastating and avoidable tragedy*. Aerospace Med. 44(5):549-551, 1973.

A detailed case history of the events surrounding an exceptionally catastrophic midair collision of two cropduster planes involved in the nighttime spraying of pesticides is reported. Killed in the accident were both pilots, as well as a woman occupying a farm home which was struck by one of the planes and subsequently destroyed by fire. The accident also precipitated two heart attacks, one of them fatal, among those witnessing the accident. A herd of dairy cattle was also contaminated by cargo spillage and debris from the crash, resulting in the death of two cows and necessitating that milk from the herd be quarantined. Some of the various problems confronting aerial applicators are also presented and discussed, as is the need for greater medical supervision of agricultural pesticide dispersal.

THE IDAHO COMMUNITY STUDY on Pesticides, sponsored by the Environmental Protection Agency, is one of 13 similar research facilities throughout the United States whose primary concern is the effects of pesticide exposure on human health. As such, our group has had a great deal of contact with aerial spray pilots, who represent one of the most intensely exposed single groups of agricultural workers in this area. Because of its speed of application, accessibility to regions difficult to spray from the ground, and economic suitability for the treatment of large areas, dispersal from aircraft has become one of the most popular means of applying agricultural materials.¹ In some areas, cropdusting is done throughout almost the entire year, and typically includes the application of such diverse items as seeds, fertilizers, herbicides, pesticides, etc. In the vicinity of southern Idaho and eastern Oregon, much of the aerial spraying of pesticides is done at night.² There are several reasons for this. In such areas where numerous seed crops are grown, spraying during daylight hours can kill bee populations, which are essential in providing pollination. Dispersing pesticides at night also tends to minimize the possibility of photodecomposition and

evaporation of the toxicants before their benefits are realized. Higher kill ratios of target pests are often achieved at night, because many detrimental insects are most active at this time. During warm sunny days, increasing surface temperatures can also cause up-drafts near the ground that can result in unwanted drifting of the spray pattern.

The task of spraying materials from an aircraft while flying only a few feet above a field often located near trees, highways, utility wires, farm buildings, animals, etc., most certainly requires meticulous preflight analysis at any time. However, despite the use of high intensity aircraft worklights and ground men with flashlights to indicate spraying paths, the aerial application of pesticides at night is an even more formidable undertaking. The nature of the cargo, which in pesticide spraying can often consist of several hundred pounds of potentially lethal chemicals, is an obvious problem. Because of bulkiness, excess warmth and decreased manual dexterity usually associated with most types of protective accessories, duster pilots may sometimes not utilize such equipment as much as would seem warranted. Should a leak or contamination somehow occur, an unprotected pilot spraying pesticides could be incapacitated in a matter of seconds. This possibility looms especially large with the advent of cholinesterase inhibitors for pesticidal use. These potent members of the organophosphate and carbamate series are currently replacing the more traditional and much less toxic organochlorines (such as DDT, aldrin, chlordane, etc.) which unfortunately are much more persistent in the environment as unwanted contaminants. Still an additional chemical factor is flammability. Most of the agricultural biocides now in common use are dispersed via a liquid carrier. Many are poorly soluble in water and are necessarily mixed in organic solvents for optimum dispersal. Melnikov⁴ cites diesel fuel, the petroleum hydrocarbons and dearomatized kerosene as among the organic solvents most frequently used in the preparation of pesticide formulations.

We report here an account of an especially spectacular and devastating cropdusting accident. It is hoped that the tragic events cited here will call attention to the potential hazards associated with the aerial spraying of agricultural chemicals and the need for their prevention.

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CASE REPORT

Shortly after 11 p.m. on Monday, Aug. 2, 1971, three aircraft were spraying alfalfa fields in a 1-mile-square area 5 miles southwest of the farming community of Nyssa, Or. Weather conditions were clear and calm with a partial moon, and none of the three pilots had been working unduly long hours prior to that time. One of the pilots, a 39-year-old man flying a Grumman Ag-Cat, G-164A, had completed the spraying of an aqueous mixture of demeton, trichlorfon and naled and was preparing to land the empty craft at a small airstrip only a short distance away. This individual had amassed a total of more than 6,500 hours flying time, 1,900 of which were in agricultural aviation. The second pilot, a 34-year-old man employed by a different company and flying from an airstrip 3 miles away, was piloting a Callair, A-9, partly loaded with demeton, trichlorfon and naled. Pilot 2 had logged 1,800 hours as a cropduster and had 7,565 hours of total flying time. The rate of application was 1 pint demeton, 1 quart trichlorfon and one-fourth pint of naled per 7 gallons of water per acre. The two planes were separated by a low ridge, preventing visual contact. The third pilot, age 25, was employed by yet another company and was spraying in the immediate vicinity from a Piper Pawnee 235. A fourth pilot, employed by the same company as Pilot 1, was parked at the loading dock at the airstrip to which Pilot 1 was returning.

At 11:16 p.m., just as Pilot 1 had nearly completed his landing approach, his plane collided with Plane 2, which had suddenly appeared from behind the ridge and was executing a tight turn prior to making another spraying pass. Neither aircraft was equipped with anticollision lights. Although both planes were equipped with high-intensity worklights and turnlights, only the navigation lights on the wings were observed by those witnessing the crash. The two aircraft collided nearly head on, crossing inside one another and shearing off their right wings. Pilot 1 was killed instantly and his plane plummeted earthward, crashing nose first some 400 feet away against an embankment in a field near the airstrip. Debris and wreckage from Plane 1 was scattered for a distance of several hundred yards in all directions. Plane 2, its pilot apparently still alive, burst into flames and continued its trajectory for about 100 yards, during which time the pilot was able to jettison his remaining cargo over a pasture. The aircraft then crashed into a home owned and occupied by a dairy farmer and his wife and four children. The plane struck the house squarely near the roof peak, exploded in flames and passed completely through the wooden frame building to lodge in the front room at the opposite corner. Killed instantly in addition to the pilot was the 44-year-old wife of the farmer, who had retired for the evening on a couch in the front room in an attempt to escape the sultry weather of early evening. Her more fortunate husband and all four children were sleeping in the rear of the building opposite the collision site and managed to flee the burning house to safety. The initial crash and its fiery aftermath were witnessed by the third pilot, who landed at once at the nearest strip and rushed to the scene.

The accident and burning farmhouse were also witnessed by the ground crews and supportive personnel for the various aircraft, as well as by several nearby residents, who notified authorities at once and attempted to render aid. One of the neighbors, a 61-year-old farm wife, suffered a fatal heart attack at the sight of the holocaust nearby and was pronounced dead at the hospital (her 65-year-old husband, himself a cardiac patient, subsequently died nearly 4 months later of a sudden heart attack, but his death had no apparent connection with the accident). Another neighbor, who coincidentally was the owner of the fields being sprayed by Pilot 2, suffered a mild anginal attack shortly after arriving at the burning home and was rushed to the hospital for treatment. Fire department personnel and helpful neighbors managed to extinguish the fires by about 11:30 p.m. but both aircraft and the farmhouse were totally destroyed, and the bodies of Pilot 2 and the farmer's wife were burned beyond recognition.

Since the field over which Plane 2 had dumped its cargo was occupied by a herd of some 40 dairy cattle, concern arose as to whether or not the animals had become contaminated from the pesticides. The cattle were seen milling about the wreckage of

Plane 1 and were moved to an adjacent field about an hour after the crash had occurred. One cow was found dead in the field about 24 hours later and another animal died some 12 hours subsequently. It was not known whether or not the spill came into direct contact with the cattle or if the animals had foraged in the tainted area. A veterinarian was summoned on Aug. 3 to examine the herd, but judged the remaining cattle to be in good health. Although the herd was milked twice each day, the accumulated milk was shipped out to the processor only on alternate days, so that each shipment from the farm represented four milkings. Milk from the herd was of "manufacturing grade" and was first combined with milk from various other dairymen and then processed into products such as butter and milk powder, rather than being marketed as whole milk. By Aug. 4, steps had been taken to quarantine all milk obtained from the herd. However, one shipment of 3,014 pounds of milk had been picked up on the morning of the previous day, and about one-fourth of this milk had thus been obtained from the animals after their alleged contamination. This shipment had already been combined with milk from numerous other farms, processed into butter and nonfat dry milk and distributed to retail outlets. (Because of dilution, however, authorities estimated that the suspected milk would have constituted only about 0.3% of the total milk processed on Aug. 3, thus minimizing any danger considerably.) Another shipment of 3,004 pounds of milk was picked up on Aug. 5, but was held at the processor until analysis and testing could be made. Gas chromatographic analysis of this shipment was negative for demeton and was within tolerance levels for trichlorfon and naled, and subsequent shipments of milk from the herd were thus cleared for processing.

DISCUSSION

Obviously, the most important factor contributing to the catastrophe reported here is that a total of four aircraft, representing three different companies, were attempting to operate in the same general vicinity at the same time. Had there been a coordinated effort among either the owners of the various fields or the spraying companies, this incident would not have happened and so many lives would not have been affected. This is especially true in view of the fact that identical cargos were being applied to identical crops by the three planes in the air at the time. Many difficulties must be overcome before such efforts can be realized. For example, because of problems involved in radio contact, it is not always easy for a given pilot to anticipate the presence of another aircraft spraying in his vicinity. At present, each spraying company is federally assigned its own particular FM broadcast frequency. Although this practice does serve to prevent the confusion which would occur if all companies shared the same frequency, it also makes it necessary for a given pilot to know the frequencies used by all other agricultural planes in his region, and to constantly vary his receiver in order to monitor them. Variable reception is currently not always possible, because some receivers are controlled by means of a fixed-frequency crystal and are thus specific for only a very narrow signal range. Differences in terrain and technological limitations of radio equipment can sometimes distort radio contact between adjacent aircraft. For example, varying meteorological conditions have precipitated incidents in which radio signals from duster pilots operating as far away as Texas have been picked up by receivers in Idaho, while broadcasts from local cropdusters only a few miles away were not audible.

Cropdusting is a buyer's market. From an economic point of view, it would be difficult for the concerned grower to align his time dependent and often complex spraying needs to coincide with those of neighboring farms, even if similar crops were involved. Another problem that can act to foster accidents is simply that many growers have fields that differ greatly in terms of size and accessibility. Such farmers are usually unwilling for example, to hire a given company to spray their hundreds of acres of open fields unless their small five-acre plot surrounded by power lines and hundred foot trees is included in the bargain. On the other hand, spraying companies must also operate from an economic viewpoint, and have little choice but to either refuse the job or take the risk. The various chemical companies involved also share some of the responsibility with regard to safe cropdusting practices. Local representatives of these companies are perhaps more familiar than anyone with the types and quantities of chemicals being applied in their areas, as well as with the various personnel and crops involved.

In many areas, personnel in aerial application programs involving pesticides are not receiving adequate medical surveillance. To our knowledge, California is the sole state presently requiring that all persons occupationally involved with organophosphates be examined at routine intervals by a supervisory physician. This usually includes the monitoring of cholinesterase activity, which has been shown to be a valuable index of excessive exposure. Whatever the solution, proper attention to and regulation of such matters is sorely needed. The use of agricultural chemicals is steadily increasing. In Idaho, Canyon County alone, which typifies a representative agricultural region only a few miles across the state line from the crash site, had more than 1 million pounds of chemicals applied to crops during 1971.³ This is an increase of 300,000 pounds over the previous year. Regrettably, safety precautions and proper attention to the judicious use of these agents have been badly outdistanced by technology. Not only does the cropdusting accident imperil the lives of its immediate participants, but also those of innocent bystanders who may become involved by circumstance. This is especially true in light of the added threat of chemical contamination.

We have previously reported an incident,⁶ in which a local duster pilot suffered a near fatal crash precipitated by his own chronic intoxication by organophosphates. Although such incidents have become all too numerous, it appears unlikely that the midair collision reported here was directly attributable to pesticide poisoning. Of the three pesticides being applied by the three pilots, the systemically acting demeton (rat² oral LD₅₀ for Demeton S: 1.7 mg/kg) is by far the most toxic. Trichlorfon and naled are also cholinesterase-inhibiting organophosphates but their oral toxicities only

approach² about 400 mg/kg. Autopsy samples of blood and adipose tissue were obtained from both pilots. Serums and fats were analyzed for pesticide residues by gas liquid chromatography, and whole bloods were examined by two methods for acetylcholinesterase activity. Although Pilot 1 had not burned, most of his body fluids had been forcibly expelled at impact and only small quantities of blood could be found. Samples from Pilot 2 were also poorly suited for analysis because of the possibility of thermal alteration. Despite these factors no abnormal pesticide residues were detected. Although whole blood cholinesterase activities were found by both methods to be depressed considerably in both men, the possibility of pesticide poisoning as a contributing factor to the collision must remain only speculative.

It is appropriate at this point to comment on the subsequent fate of Pilot 3, who continued cropdusting for the remainder of the year. On June 30, 1972, nearly 11 months after the accident, Pilot 3 crashed his empty Aero-Commander S-2R craft in a field while returning to the landing strip after spraying a cargo of the organophosphate diazinon (rat² oral LD₅₀ 150-220 mg/kg). Although he escaped the demolished aircraft with only minor injuries, Pilot 3 complained of confusion and spatial disorientation just prior to the crash, and subsequent clinical examination revealed that both his serum and RBC cholinesterase activities were depressed to subnormal levels. For some time prior to the accident, Pilot 3 had been almost exclusively applying parathion (rat oral LD₅₀ 5 mg/kg) and demeton.

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